Meta-analysis in Gastric Carcinomas

Dr Pritanjali Singh,
Associate Prof & HoD,
Radiation Oncology Dept.
All India Institute of Medical Sciences Patna.

Epidemiology.

• The incidence of gastric cancer highest in North Eastern states, such as Mizoram and Sikkim.

• Among the five most common cancers affecting young Indian men and women (age, 15–44 years).

• Second most common cause of cancer-related deaths among Indian men and women.

• A multidisciplinary approach: cornerstone in achieving the best outcome for patients with resectable gastric cancer.

Current Recommendations

<table>
<thead>
<tr>
<th>T1N0 and selective T2N0</th>
<th>SURGERY ALONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-T4/N+RESECTABLE</td>
<td>SURGERY FOLLOWED BY CTRT</td>
</tr>
<tr>
<td></td>
<td>PRE OP CT</td>
</tr>
</tbody>
</table>

| CTRT CHEMOTHERAPY ALONE |
| BEST SUPPORTIVE CARE |
| CHEMOTHERAPY ALONE |
| BEST SUPPORTIVE CARE |
| PALLIATIVE RT |


Meta-analysis is a **quantitative** approach for **systematically** combining results of **previous research** to **arrive at conclusions** about the body of research.

**Contents:**
Meta-analysis related to:

1) H. pylori eradication.
2) EUS & staging.
3) Laparoscopic Gastrectomy vs Open Gastrectomy.
4) D1 vs D2.
5) Perioperative vs adjuvant chemotherapy.
6) Adjuvant chemo radiotherapy vs chemotherapy.
7) Adjuvant chemotherapy.
8) Sx alone vs with adjuvant chemotherapy.
9) Surgery with vs. without intraperitoneal chemotherapy (IPC).
10) Efficacy and safety of Taxanes Based CT.
11) Role of Palliative RT.
12) Gastrectomy in Stage IV.
13) BSC vs Chemotherapy.

**Eradication of H Pylori and Gastric cancer?**

- Helicobacter pylori (H. pylori) is associated with an increased risk of gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphoma and a decreased risk of esophageal adenocarcinoma.

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Results:

- Eight cohort studies: 31,553 patients.
- Indicates that eradication therapy for H. pylori prevents gastric cancer.
- H. pylori eradication in relation to the risk of gastric MALT lymphoma and esophageal cancer is currently too limited to enable meta-analyses.


Studies comparing eradication therapy to no treatment & comparing successful to unsuccessful treatment.


Meta-analysis: utility of EUS for preoperative staging for gastric cancer

- Twenty-two articles
- EUS pooled accuracy for T staging was 75% with a moderate Kappa (0.52).
- EUS was most accurate for T3 disease, followed by T4, T1, and T2.
- EUS pooled accuracy for N staging was 64%, sensitivity was 74%, and specificity was 80%.
- Significant heterogeneity between the included studies.

Conclusion: EUS is a moderately accurate technique that seems to describe advanced T stage (T3 and T4) better than N or less advanced T stage.
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**EUS T4 Staging**

**EUS N staging**

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**Laparoscopic Gastrectomy (LG) vs. Open Gastrectomy (OG)**

- At least 9 meta-analyses and a Cochrane review compared the outcomes of LG versus OG.
- Number of harvested lymph nodes, OS and DFS were similar.
- Six analyses studied recurrence data and found it to be similar.
- LG had lower intraoperative blood loss, reduced risk of postoperative complications and shorter hospital stay.
- The Cochrane review also had similar findings, though the authors noted wide CIs for the parameters studied. They suggested more data be accrued before drawing a definite conclusion.

**Takeaway:** LG may considered a safe alternative to OG for AGC with a lower complication rate and enhanced postoperative recovery.
**Type of Surgery: D1 vs D2 dissection**

- Several RCT’s + least 3 meta-analyses have addressed this question.
- Individual studies have had conflicting results, with some suggesting no difference in outcomes and others vice versa.
- Meta-analyses have found a **definite trend towards improved survival** and gastric cancer related mortality with a D2 dissection.
  - In general, east Asian studies have shown improved outcomes while Western literature is more critical of the approach.

**Present consensus**: D2 dissection should be done wherever the experience and post-operative care is available to manage the greater morbidity associated with it (ESMO, NCCN).

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**NEoadjuvant/perioperative vs adjuvant ??**

**3 Major Trials**

**MAGIC**

French FNLCC/FFCD

**EORTC 40954**

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**MAGIC Trial**

**Eligibility Criteria**

- ANY AGE
- T2 OR HIGHER
- PS: 0 OR 1
- ADENOCARCINOMA OF STOMACH OR DISTAL ESOPHAGUS
- NO EVIDENCE OF DISTANT METASTASIS

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Perioperative chemotherapy & Surgery only

<table>
<thead>
<tr>
<th>Infusional 5FU</th>
<th>Epirubicine</th>
<th>Cisplatin</th>
</tr>
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<tbody>
<tr>
<td>250 patients</td>
<td>253 patients</td>
<td></td>
</tr>
</tbody>
</table>

TOTAL 503 PATIENTS

5 yr survival 36% Vs 23%

SUMMARY

- OS and PFS: Significantly better with perioperative chemotherapy.
- Estimated improvement in 5-year survival: 13% (23% → 36%).
- Local failure and distant metastases were both lower 14% Vs 21% & 24% Vs 37% respectively.

Limitations of Magic Trial:

- Non standardized surgery
- Inaccurate preoperative staging
- Higher proportion of patients in chemotherapy arm undergo potentially curative surgery (79% VS 70%).
- More patients in the chemotherapy arm had lower stage disease: T1/2 (52 vs 37%) and N0/1 (84 vs 71%).
- Only 104 (42%) patients were able to complete protocol treatment.

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FRENCH FNCLCC TRIAL

November, 1995 - December, 2003

All patients underwent D2 resection which is the standard surgical procedure in gastric carcinoma.

CHEMOTHERAPY USED WAS CISPLATIN AND 5FU

<table>
<thead>
<tr>
<th>5YR DFS</th>
<th>5YR OS</th>
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<tbody>
<tr>
<td>34% VS 19%</td>
<td>38% VS 24%</td>
</tr>
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</table>

AFTER MEDIAN FOLLOW UP OF 5.7 YEARS

- Significant improvement in DFS and OS with perioperative chemotherapy.
- Most common toxicity: Neutropenia and nausea/vomiting.

Neoadjuvant chemotherapy (NACT) vs. Upfront Surgery

- Two meta-analyses compared the outcomes of surgery in combination with NACT versus no therapy before surgery.
- Both of them favored NACT in terms of OS.
- One of them also favored NACT in terms of 3-year PFS.
- Both meta-analyses demonstrated that the resection rate was higher for NACT group than for control group while the perioperative mortality was similar.
- One of them also noted that NACT had a significant downstaging effect on AGC.
- NACT could improve the tumor resection rate and the survival rate in AGC patients without increasing the operative risk.
Meta-analysis regarding NACT

- NACT associated with significant OS & PFS improvement.
- NACT: TT R0 Resection rate.
- No worsening of operative complications, perioperative mortality, or grade 3 or 4 adverse effects.


- 11 studies: Five RCT + six clinical controlled trials (1,240pts).
- First metaanalysis that compares PC with AC in GC.
- PC vs AC had significantly better prognosis (HR, 0.74; 95 % CI, 0.61 to 0.89; P < 0.01).
- NAC: better in
  - Comb chemotherapy: (HR, 0.59; 95 % CI, 0.46 to 0.76; P < 0.01) vs
  - 5FU monotherapy: (HR, 0.93; 95 % CI, 0.56 to 1.55; P = 0.84)
- PC group trend towards a ↑radical resection rate (RR, 1.10; 95 % CI, 0.96 to 1.27; P = 0.17)
- No significant differences in the post-operative complication rates (relative risk, 0.98; 95 % CI, 0.63 to 1.51; P = 0.91)
- Adverse effects: not significantly different between the two study groups (P > 0.05 for all the comparisons.)

RCT vs CCT

China vs Japan

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**NAC Regimen**

- **Monotherapy**
- **Combination CT**

NAC significant better in the studies that used Combination chemotherapy: (HR, 0.59; 95% CI, 0.46 to 0.76; P < 0.01) vs Fluoropyrimidine monotherapy: (HR, 0.93; 95% CI, 0.56 to 1.55; P = 0.84)

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**Meta-analysis of Hazard ratio for radical resection rate.**

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**Meta-analysis of postoperative complication rate.**

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**Adjuvant Chemoradiation**

- **3 RANDOMIZED TRIALS**
- **INT 0116/ SWOG 9008**
- **Macdonald regimen**
- **CALGB 80101**
- **ARTIST**

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STUDY DESIGN

DAY 1 TO 5
LEUCOVORIN (20mg) AND 5 FLUOROURACIL (425mg)

DAY 28

FU 400 mg/m²/d and LV 20 mg/m²/d was given the first four and the last three days of radiotherapy.

1 MONTH AFTER RT

5 Yr OS
43% Vs 28%
IN FAVOUR OF CTRT

3 Yr DFS
48% VS 31%
IN FAVOUR OF CTRT

DISTANT RELAPSE
WAS 16% VS 18%
REGIONAL
RELAPSE WAS 22%
VS 39%

RADIOCHEMOTHERAPY CONSISTED OF BOLUS FLUOROURACIL AND LEUCOVORIN BEFORE, DURING, AND AFTER RADIOTHERAPY.

T3 or higher
And/node +ve
R0 resection

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Even after 10 years of follow up the survival advantage with CTRT is better than surgery alone.

- 3yr OS was 50% vs 41%
- 3yr RFS was 48% vs 31%
- Toxicity was more with CTRT.

Conclusion:
- CTRT significantly decreases the locoregional Failure.

Limitations:
- D2 dissection was only performed in 10% of cases.
- Only 64% of cases completed the treatment and 17% discontinued treatment due to toxicity.

Postop adjuvant chemoradiation for gastric or GE junction Adeno Ca
Intergroup CALGB 80101

Randomize

S-FU/LV  →  S-FU IVCI  →  S-FU/LV
X1       RT        X2

ECF     →  S-FU IVCI  →  ECF
X1       RT        X2

S-FU/LV: S-FU 425 mg/m² d1-5, LV 20 mg/m² d1-5
RT: 45 Gy (1.8 Gy X 25 fractions) with S-FU 200 mg/m² CI
ECF (pre-RT): Epirubicin 50 mg/m² d1, Cisplatin 60 mg/m² d1, & S-FU 200 mg/m² d1-21
ECF (post-RT): Epirubicin 40 mg/m² Cisplatin 50 mg/m² S-FU 200 mg/m² CI d1-21

NO DIFFERENCE IN OS
P=0.80

NO DIFFERENCE
IN DFS
P=0.99

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ARTIST

458 pts
SURGERY WITH D2 LN DISSECTION

CAPECITABINE AND CISPLATIN 6 CYCLES

CAPECITABINE AND CISPLATIN 2 CYCLES

XPRT 45Gy IN 2SF

CAPECITABINE AND CISPLATIN 2 CYCLES

NO DIFFERENCE IN DFS & OS

- Subset analysis indicate a significantly better DFS with chemoradiotherapy in those with node-positive disease (three-year DFS 76 versus 72 %, p = 0.004).

META-ANALYSIS Major Randomized Trial of Chemo radiotherapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Name</th>
<th>NOS/C08Loc</th>
<th>Randomization</th>
<th>Primary Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>NOS/SMC</td>
<td>surgery D2</td>
<td>2 gy + capecitabine</td>
<td>3-year OS</td>
<td>Median OS 28 vs 47%</td>
</tr>
<tr>
<td>Trial 2</td>
<td>SMC</td>
<td>surgery D2</td>
<td>capecitabine/XPRT</td>
<td>3-year OS</td>
<td>35 vs 40.9%</td>
</tr>
<tr>
<td>Trial 3</td>
<td>SMC</td>
<td>surgery D2</td>
<td>2 gy + capecitabine</td>
<td>3-year OS</td>
<td>35 vs 40.9%</td>
</tr>
<tr>
<td>Trial 4</td>
<td>SMC</td>
<td>surgery D2</td>
<td>2 gy + capecitabine</td>
<td>3-year OS</td>
<td>35 vs 40.9%</td>
</tr>
<tr>
<td>Trial 5</td>
<td>SMC</td>
<td>surgery D2</td>
<td>2 gy + capecitabine</td>
<td>3-year OS</td>
<td>35 vs 40.9%</td>
</tr>
</tbody>
</table>

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Adjuvant Chemotherapy

2 TRIALS

JAPANESE S-1 trial

CLASSIC trial

JAPANESE S-1 TRIAL

Stage II, III
Potentially resectable
Sx with D2 lymphadenectomy

S1: 3 drug combination with principal agent tegafur.

OS

Primary end point: OS
Median FU: 5 years

<table>
<thead>
<tr>
<th>Results</th>
<th>Surgery + adjuvant S-1</th>
<th>Surgery alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>71.7%</td>
<td>61.1%</td>
</tr>
<tr>
<td>RFS</td>
<td>65.4%</td>
<td>53.3%</td>
</tr>
</tbody>
</table>

Conclusion: Adjuvant S1 improves survival for Stage II/III gastric cancer.
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**CLASSIC TRIAL**

- **Randomize**
  - 1035 pts
  - Surgery with D2 LN dissection
  - At least 15 LN extracted
  - **Capecitabine and Oxaliplatin 8 Cycles**
    - 520 patients: Capecitabine 1000mg/m² D1-14, Oxaliplatin 130 mg/m²
    - No adjuvant therapy
    - 515 patients

**CAPECITABINE AND OXALIPLATIN 8 CYCLES**

- 3 YEAR DFS 74% VS 59%
- 3 YEAR OS: 83% VS 78%
- 5 YEAR OS: 78% VS 69%

*P < 0.0001*  
*P = 0.0493*

9 TIMES MORE GRADE 3 & 4 TOXICITIES IN CT ARM.  
ONLY 67% OF PATIENTS RECEIVED ALL 8 CYCLES OF CT.  
90% OF PATIENTS REQUIRE CT DOSE MODIFICATION.

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**Meta-analysis : Adjuvant Chemotherapy**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Journal (year)</th>
<th>Comparisons</th>
<th>DFS, OS, PFS, Recurrence, TTF, TTP</th>
<th>Other</th>
<th>Major Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun J</td>
<td>BMC Cancer (2013)</td>
<td>Palliative gastrectomy with vs. without AC</td>
<td>Favour palliative gastrectomy with AC</td>
<td>NA</td>
<td>Palliative gastrectomy might improve survival</td>
</tr>
<tr>
<td>Sun P</td>
<td>Br J Surg (2009)</td>
<td>Surgery with vs. without AC</td>
<td>Favour surgery with AC</td>
<td>NA</td>
<td>Postoperative chemotherapy could improve OS after radical surgery for gastric cancer</td>
</tr>
</tbody>
</table>
Surgery with vs. without intraperitoneal chemotherapy (IPC)

- **Two meta-analyses** compared the outcomes of surgery combined with IPC versus surgery without IPC.
- One of the meta-analyses revealed IPC significantly **improve 1-, 2-, 3-year OS** but not 5-year OS.
- Another meta-analysis on adjuvant IPC demonstrated that hyperthermic intraoperative intraperitoneal chemotherapy (HIIPC) with or without early postoperative intraperitoneal chemotherapy (EPIPC) after gastrectomy was associated with **improved OS**; Best therapy in Positive peritoneal metastasis.

### Meta-analysis: Surgery with or without IPC

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Comparator</th>
<th>Surgical plus vs. without IPC</th>
<th>OS/DFS/RFS/PFS, Recurrence, T, Other Major Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coccolini F (16)</td>
<td><strong>Eur J Surg Oncol</strong> 2014</td>
<td>Surgery with vs. without IPC</td>
<td>Favour surgery+IPC; 1,2,3-year: statistically similar; Other Major Comments</td>
<td>Overall recurrence, peritoneal recurrence, haematogenous metastasis: favour surgery+IPC; Lymph nodal recurrence: statistically similar; Mortality:1-,2-,3-year: Favour surgery+IPC; 5year: Statistically similar; 2-,3-year in patients with loco-regional nodal meta-tastasis, 1,2-year in patients with serosal infiltration: favour surgery+IPC; Morbidity: higher in surgery alone. IPC had positive effect on peritoneal recurrence and distant metastasis. Locoregional lymph-nodes invasion in patients affected by AGC was not a contraindication to IPC.</td>
</tr>
<tr>
<td>Yan TD (58)</td>
<td><strong>Ann Surg Oncol</strong> 2007</td>
<td>Surgery with vs. without IPC</td>
<td>Favour surgery with HIIPC or EPIPC (but statistically similar between surgery with NIIPC, EPIPC or DPIPC and surgery without IPC)</td>
<td>Peritoneal recurrence (surgery with HIIPC or NIIPC vs. control): statistically similar. Perioperative mortality: statistically similar. Risk of intra-abdominal abscess, neutropenia: higher in IPC+ surgery. HIIPC with or without EPIPC after resection of AGC improved the overall survival. However, increased risk of intra-abdominal abscess and neutropenia were also demonstrated.</td>
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</table>

- **Intraoperative intraperitoneal chemotherapy (IIPC)** with **adjuvant chemotherapy** showed a trend toward **improvement in overall survival** (HR 0.70; 95% CI 0.47–1.04; p = 0.08).

- A recent randomized controlled trial examining extensive intraperitoneal lavage (EIPL) with IIPC showed a significant improvement in overall survival (5-year overall survival, 43.8% for EIPL-IPC group compared with 4.8% for IPC group).

- Given its superiority in the quantity of RCT studies, the results of the meta-analysis by Coccolini might be more reliable.

- Locoregional Lymph node invasion was not a contraindication

- **Conclusion:** IPC had **positive effect** on overall and peritoneal recurrence and distant metastasis.
Advanced Gastric Cancer
Unresectable, recurrent and/or metastatic disease

Chemotherapy
Advanced Gastric Cancer: Taxane based CT

- In the palliative setting, 5FU based regimens are mostly employed, but taxanes are now increasingly being used by several researchers.
- Shi et al analyzed data from 11 studies (6 randomized, 5 non-randomized) and evaluated data from 1932 patients and compared:
  1. Non taxane regimen vs same regimen + Taxane
  2. Taxane vs non taxane chemotherapy
- 1st comparison: OS, PFS and Overall response rate (ORR) were all better with taxane.
- 2nd comparison: PFS and ORR was better but not the OS. Toxicity was higher with taxanes, but not significantly so.

Conclusion: Adding taxanes to current first-line treatment options for AGC can improve OS, PFS, and ORR; however, these increase the risk of toxicity and options should be discussed with the patient.

Chemotherapy
Advanced Gastric Cancer: Cisplatin or not?

- 5-FU based chemotherapy is the main treatment for advanced gastric cancer and has been demonstrated to improve OS in a Cochrane analysis.
  - Studies have shown that adding other agents (other than cisplatin) also improves outcomes, most notably oxaliplatin.

- Petrelli et al compared Cisplatin based regimens to chemotherapy in which Cisplatin was replaced by a different drug.
  - 14 studies (5 randomized, 9 phase II), 2981 patients
  - They found non-cisplatin regimens to have significantly better outcomes:
    - OS: HR 0.79, 95% CI 0.68 – 0.92
    - PFS: HR 0.77, 95% CI 0.66 – 0.90

Conclusion: Combination chemotherapy in which cisplatin is replaced by new drugs improve outcomes and should therefore be strongly considered in the metastatic setting.
Role of Palliative RT

- A meta-analysis of 7 studies of palliative RT
- Various dose-fractionation schedules.
- Bleeding: No difference in response rate (BED) of ≥ 39Gy vs low BED < 39Gy.
- Upto 15% patients had Grade 3+ toxicities.

<table>
<thead>
<tr>
<th>ORR</th>
<th>Bleeding</th>
<th>74%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Obstructive symptoms</td>
<td>68%</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: More than two-thirds of patients receiving RT in the palliative setting would have a benefit, and low BED regimens appear to be adequate for symptom palliation.

Gastrectomy for Stage IV Gastric Cancer
A Systematic Review and Meta-analysis

- 50% patients with non-resected advanced gastric carcinoma develop severe tumor-related complications that may merit surgical resection.
- Lasithiotakis et al: 19 studies (2911 patients) who underwent local surgery as a part of treatment for metastatic disease.
- Patients who underwent resection had a better 1 year OS vs conservative management (OR 4.9, 95% CI 3.2-7.5), and also when compared to non resectional treatment (OR 2.6, 95% CI 1.7 – 4.3).
- However, this is all from non-randomized data.

Conclusion: Benefit cannot be ruled out, but no randomized evidence at present; not routinely recommended.

Chemotherapy vs. basic supportive care (BSC)

- In patients with relapsed/poorly responding disease, several studies have shown that there is an OS benefit with second line chemotherapy.
  - A meta-analysis of 3 such studies (Jawed et al, 2016) was done on patients who had failed after 1st line chemotherapy with CDDP/5FU-based regimens.
  - 2nd line chemotherapy significantly improved OS (HR for death 0.63) and older patients with a better PS and non-metastatic disease have a better outcome.
  - QoL data was reported in only one of the studies.
- For third line chemotherapy, Chan et al published a review of 6 studies involving 880 patients.
  - They reported a significant, though small OS benefit (3.2m → 4.8m). PFS, ORR and disease control rate were also better. QoL data was, however, not reported.
- Second and 3rd line chemotherapy does provide benefit, but an analysis is required to assess the cost and morbidity associated with it.

Conclusion: Can consider 2nd/3rd line chemotherapy; especially for patients with a good PS. Patient should be involved in the decision making process.
CONCLUSION

• Multimodality treatment (MMT) should be the norm for management of gastric cancer.
• For locally advanced disease, gastrectomy remains the mainstay of treatment. Laparoscopic gastrectomy with D2 nodal dissection should be considered standard of care.
• Adjuvant treatment improves outcomes for advanced disease.
  - D1 or D0 nodal dissection: Chemoradiotherapy (CRT)
  - D2 dissection: CRT if node positive, chemotherapy alone if node negative.
• Neoadjuvant/perioperative chemotherapy should be considered for resectable disease. For unresectable disease, Neoadjuvant CRT will often provide the opportunity for a curative resection.
• All 3 treatment modalities have a role in palliation; chemotherapy and radiotherapy more so than surgery.

THANK YOU