“Anal cancer chemoradiotherapy”
Evidence and guidelines

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Background

- Carcinomas in the anal canal account for about 1.5% of gastrointestinal cancers in the United States, and approximately 80% of these are squamous cell carcinomas (SCCs).
- SCCs of the anus are frequently related to chronic infection with human papilloma virus (HPV).
Background

- Usually occur in the sixth to seventh decade of life
- Occur in younger patients when immuno compromised
- Male:Female=2:1
- HIV/AIDS, and the increasing use of immunosuppressive therapy for solid organ transplantation, inflammatory bowel disease and collagen vascular diseases has meant an increasing incidence of HPV infection and anal SCC
Anal tumours - pathology

- SCC
- Basaloid*
- Cloacogenic (transitional)*

SCC : 80%

- Adenocarcinoma
- Melanoma
- Sarcoma
- Lymphoma
- carcinoid
- Undifferentiated

* Variants of SCC.
Anal Cancer: Just the Facts

- **Anatomy:**
  - 3-4 cm anal canal
  - Anal verge to dentate line

- **Lymph node drainage:**
  - Perirectal
  - Internal iliac
  - Inguinal nodes

(Up-to-date; cancerbackup.org)
Anal tumours - staging

- History
- Examination in clinic if possible – abdo / groins / PR
- EUA with biopsy
- ? FNA of any groin nodes
- CT scan
- MRI scan
- (Endoanal U/S)
Utility of Other Tests

- PET scans
  - Nagle – 14 patients
    - Sensitivity = 50%, specificity = 72%, predictive value positive (PVP) = 50%, predictive value negative = 80%
  - Trautman – 24 patients
    - 24% had disease not seen on CT scans
  - Cotter – 41 patients
    - 20% had groin nodes negative on CT scan
    - 23% had groin nodes negative on physical examination
    - 91% had primary tumor identified vs. 59% on CT scan

- Ultrasound
  - Giovanni – 146 patients
    - Advantage was in determining complete response
Anal canal - TNM

- Tis: carcinoma *in situ*
- T1: tumour 2cm or less
- T2: tumour 2 - 5cm
- T3: tumour 5cm or more
- T4: tumour invading adjacent organs

- N0: No nodes
- N1: perirectal LN metastases
- N2: unilateral int iliac ± inguinal LN
- N3: bilateral int iliac + ing and perirectal LN
Surgical Treatment

• Abdominoperineal resection
  – Local failures range from 27-47%
  – 5-year survivals range from 50-70%
Radiotherapy: Reasonable alternative to surgery

Radiation therapy alone:

- 5 year survival: 39 - 76%
- Colostomy-free survival: 67 - 74%
- Doses ≥ 60 Gy: necrosis and fibrosis

Combination Therapy – Wayne State

- 1970s - investigators preoperatively administered fluorouracil and mitomycin combined with RT to decrease the surgical failure rate:
  - 5-FU (1000 mg/m² per day, days 1-4 & 29-32)
  - Mitomycin (10 to 15 mg/m², day 1 only)
  - Intermediate dose RT (30 Gy in 15 fractions via AP/PA fields to the true pelvis, medial inguinal LN, and primary lesion with margin)

- Surprisingly, first 3 patients had no residual tumor when abdominoperineal resection was performed

- Suggested it might be possible to cure anal cancer without permanent colostomy

Anal chemoradiotherapy

There have been many small trials using different forms of chemotherapy with varying types of radiotherapy

Started by Nigro in 1973

1980’s….primary treatment started moving away from the surgeons
<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Details</th>
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<tbody>
<tr>
<td>UKCCR ACT 1</td>
<td>CRT vs RT</td>
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<tr>
<td>EORTC 22861</td>
<td>CRT vs RT</td>
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<tr>
<td>RTOG 8704/ECOG</td>
<td>Role of MMC</td>
</tr>
<tr>
<td>RTOG 98-11</td>
<td>Role of NACT/cisplat</td>
</tr>
<tr>
<td>ACCORD-03</td>
<td>Role of NACT cisplat/ RT</td>
</tr>
<tr>
<td>CRUK ACT 2</td>
<td>Role of cisplat vs MMC</td>
</tr>
<tr>
<td>EORTC 22011-40014</td>
<td>Role of 5FU vs CDDP/MMC not extended to phase III</td>
</tr>
</tbody>
</table>
Anal chemoradiotherapy

- UKCCCR Anal Canal Trial 1 – 577 pts (ACT1) \(^1\)
- EORTC trial – 110 pts \(^2\)

\(^1\) Lancet 348: 1049-1054, 1996
\(^2\) Bartelink et al, JCO, 15:2040-2049, 1997
UKCCCR Anal Cancer Trial (ACT 1)

- RT alone 45Gy
- Boost 25Gy implant or 15Gy in 6F (6 weeks)

- CMT – 45Gy + Mitomycin C 5FU
- Boost 25Gy implant or 15Gy in 6F (6 weeks)
ACT I: Time to first local relapse

Percentage of patients having a local relapse (%)

Time since randomisation (years)

- RT alone
- CMT
Colostomy-free survival

- **RT alone**
  - 5-year: +10.1% (3.3 – 16.6)
  - 10-year: +10.0% (3.1 – 16.9)
  - 12-year: +9.5% (2.9 – 16.4)

- **CMT**

Number at risk:
- RT alone: 285 132 101 86 64 47 31 24 12
- CMT: 292 178 147 130 98 62 42 20 8
Figure 2: Overall survival, by treatment
The estimates shown are the absolute risk differences: CMT minus RT alone (95% CI)

Number at risk:
RT alone: 285 199 149 126 94 65 39 30 14
CMT: 292 221 175 153 115 78 56 30 12
UKCCCR ACT 1 trial

- RT ± MMC and 5FU chemotherapy
  - 45Gy phase I and then 15 Gy boost
  - MMC 12mg/m² d1; 5FU 1g/m² d1-4 and d29-32

- 577 pts

- Median FU of 42 months (3 ½ years)

- Local failure: RT 61% (p<0.0001)
  - CRT 39% (46% reduction in risk of failure)

Lancet 348, 1049-1054, 1996
UKCCCR ACT 1 trial........but.......... 

• 46% had local treatment failure (265/577)
• Of these, 58% were considered suitable for salvage surgery
• The remaining 42% had a range of palliative treatments
• 50% were dead at 5 years (51 and 52% in each arm) *

Therefore anal cancer is not as treatable as some people may think. However, there is a chance of survival without colostomy which is not possible with primary surgery

* Remember APR: 5 yr survival N0 50-70%, N+ 20%.
Anal verge - treatment

- Local resection with close FU
  (up to 80% 5 year survival)
- AP resection
- Chemoradiotherapy
Anal canal (N0) - treatment

- AP resection

- Chemoradiotherapy *

  * ? Defunctioning colostomy required
  * ? Anal canal damaged anyway and colostomy would be required even if tumour cured by CRT
Radiotherapy for Anal SCC

No standard approach

- External beam alone with external beam boost *
  (* photon or electron)
- External beam with brachytherapy implants
- Electron beam or brachytherapy only
ACT II

Patients with confirmed primary epidermoid anal cancer with
(Staged and biopsied by EUA & CT Scan)

GFR ≥ 50 ml/min

RANDOMISE*

RT + 5-FU + MMC

RT + 5-FU + MMC

RT + 5-FU + CDDP

RT + 5-FU + CDDP

No Maintenance Therapy

Maintenance Therapy (2 courses of 5-FU + CDDP)

No Maintenance Therapy

Maintenance Therapy (2 courses of 5-FU + CDDP)

? Cisplatin better than MMC
? Maintenance therapy beneficial
Chemoradiation Regimens

RT week 1 2 3 4 5 6

5FU

1000mg/m² d1-4 & 29-32
24-hour continuous iv infusion

12mg/m² d1 only
iv bolus, max single dose 20 mg

MMC

RT week 1 2 3 4 5 6

5FU

1000mg/m² d1-4 & 29-32
24-hour continuous iv infusion

CisP

60mg/m² d1 & 29
iv infusion
ACT II Endpoints

Chemoradiation (CRT) comparison
Primary Endpoints
• Complete response rate at 6 months
• Acute Toxicity (CTC Grade 3 & 4)

Maintenance comparison
Primary Endpoint
• Recurrence Free Survival

Both comparisons
Secondary Endpoints
• Colostomy Rate
• Cause-specific & Overall survival
ACT II - Radiotherapy

• 50.4 Gy in 28 fractions in total (1.8Gy/#)
• 2 phase treatment – no gaps *

* Constantinious *et al*, 1997: Trend towards improved 5 year survival when treatment completed within 40 days (86% vs 60%, p=0.14).
ACT II – Phase 1

• Large Ant/Post Parallel Opposed Portals
  – include all macroscopic disease
  – include both inguino-femoral regions
• Prone
• 3060 cGy in 17 fractions

- Hu et al, 1999: 30-34Gy vs 50.4Gy for presumed microscopic residual disease following excision biopsy; no difference in local control.
- Newman et al, 1992: 62 pts with no clinical or radiological evidence of groin nodes – only 5 relapsed at this site – all salvaged by groin dissection
Phase I - Parallel opposed fields 30.6 Gy in 17 daily fractions

Sup border
2 cm above bottom of SI joints

Inf border
3 cm below anal margin (canal only tumours) or 3 cm below most inferior extent of tumour (anal margin tumours)

Lateral border
Lateral to femoral head to cover inguinal nodes

Marker on inferior extent of tumour (margin tumour)
Marker on anal verge (canal only tumours)
ACT II – Phase 2

- Planned simultaneously with phase 1.
- Simulator or CT planning.
- **1980 cGy in 11# (1.8Gy/#).**
- All visible tumour marked using radiopaque marker (with rectal contrast in orthogonal films).
- 3 or 4 field plan.
Phase II - 19.8 Gy in 11 daily fractions planned volume

N0 patients (anal canal tumours) - field borders
Positive inguinal nodes
(10% of pts)

- Chemoradiotherapy
- Also consider:
  - Primary surgery to both sites
  - Combination of surgery and CRT (RT dose may need to be lower and neo-adjuvant chemotherapy may be appropriate)

- Ask:
  - is this palliative or radical treatment
75 year old lady with N3 disease
Phase II - 19.8 Gy in 11 daily fractions parallel opposed fields N+ patients

Sup field border
3 cm above most superior extent of GTV

Inf field border
3 cm below anal margin (canal only tumours) or 3 cm below most inferior extent of tumour (anal margin tumours)

Lateral field border
3 cm lateral to most lateral GTV
# Tumour Stage

<table>
<thead>
<tr>
<th>T stage</th>
<th>MMC (472)</th>
<th>CisP (468)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 T2</td>
<td>49% (232)</td>
<td>54% (254)</td>
</tr>
<tr>
<td>T3 T4</td>
<td>48% (225)</td>
<td>44% (205)</td>
</tr>
<tr>
<td>TX</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>N Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>63% (297)</td>
<td>62% (290)</td>
</tr>
<tr>
<td>Node positive</td>
<td>32% (150)</td>
<td>33% (155)</td>
</tr>
<tr>
<td>NX</td>
<td>25</td>
<td>23</td>
</tr>
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</table>
Response at 26 weeks

<table>
<thead>
<tr>
<th>Patients with response data (863)</th>
<th>MMC (432/472)</th>
<th>CisP (431/468)</th>
<th>P=0.66</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR primary</td>
<td>90%</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>CR N0</td>
<td>83% (358)</td>
<td>84% (362)</td>
<td></td>
</tr>
<tr>
<td>CR N+</td>
<td>3% (15)</td>
<td>3% (12)</td>
<td></td>
</tr>
<tr>
<td>CR Nx</td>
<td>4% (18)</td>
<td>3% (12)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>3% (14)</td>
<td>6% (24)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1% (5)</td>
<td>1% (6)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>5% (22)</td>
<td>3% (15)</td>
<td></td>
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</table>
ACT II Compliance & Toxicity

• Radiotherapy
  – 92% MMC vs 90% CisP - total dose 50.4Gy
  – ~3% >7 days interruptions

• Chemotherapy - weeks 1 & 5
  – 75% MMC vs 72% CisP full dose weeks 1 & 5

• Acute toxicity
  – 58% MMC vs 60% CisP Grade 3
  – 13% MMC vs 12% CisP Grade 4
  – 71% MMC vs 72% CisP combined Grade 3/4
### CR at 26 weeks

<table>
<thead>
<tr>
<th>Group</th>
<th>Difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC</td>
<td>CisP</td>
<td></td>
</tr>
<tr>
<td>83% (358/432)</td>
<td>84% (362/431)</td>
<td>+1% (-3.8 to 6.1)</td>
</tr>
<tr>
<td>No Maint</td>
<td>Maint</td>
<td></td>
</tr>
<tr>
<td>82% (337/409)</td>
<td>85% (348/410)</td>
<td>+3% (-2.6 to 7.5)</td>
</tr>
</tbody>
</table>
ACT II – Conclusions

- Excellent CR rate at 6 months - 83% v 84% - no difference MMC/Cisp
- No difference in colostomy rate
- No difference in PFS
- 60% of pts not in CR at 11 weeks achieved CR at 26 weeks.
- We recommend assessment at 26 weeks in future trials
Event is progression, recurrence or death

HR: 0.94, 95% CI: 0.72 to 1.24, P=0.67

No Maint - 103 events
Maint - 100 events

<table>
<thead>
<tr>
<th>Time from randomisation (years)</th>
<th>No Maint</th>
<th>Maint</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>472</td>
<td>468</td>
</tr>
<tr>
<td>1</td>
<td>346</td>
<td>345</td>
</tr>
<tr>
<td>2</td>
<td>263</td>
<td>251</td>
</tr>
<tr>
<td>3</td>
<td>183</td>
<td>183</td>
</tr>
<tr>
<td>4</td>
<td>116</td>
<td>132</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>61</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
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</table>
Maintenance Comparison - Overall Survival

Overall survival (%)

HR: 0.81, 95% CI: 0.57 to 1.13, P=0.21

No Maint - 74 events
Maint - 60 events

Overall survival (%)

No. at risk

No Maint
446 369 278 198 125 67 19 4
448 361 278 203 138 71 22 3

Time from randomisation (years)
ACT II – Conclusions 2

Maintenance comparison

• Preliminary data shown 2009
• Median follow-up now 5 years
• No evidence of any difference in PFS, cause specific survival or overall survival
ACT II Timing of pelvic recurrences
(93% in years 1-3)
• Locally advanced >4cm or N1 anal canal
• Therapeutic intensification
  – Induction chemotherapy
  – High dose radiotherapy
• Primary endpoint: colostomy-free-survival (CFS).
• Secondary endpoint: QOL, local control (LC), overall survival (OS), and cancer-specific survival.
ACCORD 03

R

CT
CDDP 5FU 2 cycles

No CT

CT
CDDP 5FU 2 cycles

No CT

CT
CDDP 5FU 2 cycles

No CT

low boost
15 Gy

high boost
20-25 Gy

45 Gy
CDDP 5 FU 2 cyc

45 Gy
CDDP 5 FU 2 cyc

45 Gy
CDDP 5 FU 2 cyc

45 Gy
CDDP 5 FU 2 cyc

5 years CFS

70%  82%  77%  73%
RTOG 9811 Time to Colostomy

RTOG 9811 Ajani JA et al JAMA 2008
RTOG 9811
Disease Free Survival

No. at risk
Mitomycin group  324  226  150  114  76  34  10
Cisplatin group   320  223  160  104  62  34  18

Log-rank $P = .17$
Is the Mitomycin C Necessary? Results of RTOG 87-04/ECOG 1289

- 30.6 Gy to pelvis + boost to 50.4 Gy
- 5-FU 1000 mg/m²/d × 4 wk 1 and 5
- Mitomycin C: 10 mg/m² × 2
- 9 Gy with 5-FU & cisplatin for salvage after positive biopsy

<table>
<thead>
<tr>
<th></th>
<th>FU+MMC</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ biopsy at 6 weeks</td>
<td>7%</td>
<td>15%</td>
</tr>
<tr>
<td>5-year colostomy rate</td>
<td>11%</td>
<td>22%</td>
</tr>
<tr>
<td>DFS</td>
<td>67%</td>
<td>50%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>23%</td>
<td>7%</td>
</tr>
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</table>

What do you do T4 or locally extensive disease?
T4 disease

- Surgery
- Chemoradiotherapy
- Both of the above - ? sequence
North-west anal cancer audit

- 254 patients (50% RT, 50% CRT) in 12 years (1998 – 2000)
- RT alone mainly given to elderly / frail patients
- 99 (39%) local disease failures (RT 60%, CRT 39%)
  - 94 (95%) occurred within 3 years of treatment
- 3 yr LD failure rate of 49% (RT) and 30% (CRT)
- 73 out of the 99 failures underwent salvage surgery (74%)
- 5 year survival – overall: 52% (CRT – 56%; RT 49%)
- 5 year survival after disease failure: 29% (40% for op pts)

The survival of patients that recur locally is poor and salvage surgery is not always possible and is difficult

Patterns of local disease failure and outcome after salvage surgery in pts with anal cancer. Renehan, Saunders, Schofield, O’Dwyer; BJS, 2005
What do you do if the disease is too extensive to treat or if metastatic disease is evident?
42 year old man with T4N3 disease
Neo-adjuvant* / palliative chemotherapy

- MMC
- 5FU (capecitabine)
- Cisplatin

* And then surgery or chemoradiotherapy
What do you do for patients with anal cancer and connective tissue diseases?
Anal cancer / SLE / Immunosuppression

- AP resection

- Chemoradiotherapy
  - But proceed with caution after discussing the case with the rheumatologist and stopping / reducing the immunosuppressant if possible. Keep the treatment volume as small as possible. Probably tamper the chemo doses.

Anal Canal Cancer and Chemoradiation Treatment in Two Patients with SLE treated by Chronic Therapeutic Immunosuppression
Khoo, Saunders, Gowda, Price, Cummings; Clinical Oncology, 2004.
IMRT in anal cancer

• New application gaining support
• Studies show reduced toxicity rates with comparable local control and survival statistics.
• *Chen et al.* Conventional AP/PA pelvic fields vs. Conformal avoidance IMRT planning
  – Comparable PTV coverage:
    • IMRT plan: 97-98% of PTV at 90% prescribed dose
    • Conventional AP/PA: 94% of PTV at 90% prescribed dose
  – IMRT spared femoral heads 58-59% vs. 71-72% of prescribed dose and genitalia 55-63% vs. 78-97% with conventional planning
Multicenter experience with IMRT for anal cancer

• 53 patients treated at three academic medical centers with IMRT and chemotherapy for definitive treatment of anal cancer.

• Response
  – Complete response in 92%
  – Local recurrence rate 13% @ 18 months
  – 18-month colostomy free survival 83.7%
  – 18-month distant recurrence free survival 92.3%

(Salama et al., 2007)
Thoughts

• No longer feasible to think that one size fits all in anal cancer
• We improved
  overall 3 year DFS from 54% (ACT I)
  to 74% (ACT II)
• We took 7 years to do ACT II
• We probably need international collaboration for next studies
Radiotherapy strategies which need exploring

- Optimization of radiotherapy
  (optimal dose/ fractionation/ concomitant boost/ brachytherapy)
- Optimal field sizes
- Evaluation of new radiosensitization protocols
  (oxaliplatin, irinotecan, taxanes)
- Optimization of radiotherapy techniques
  (IMRT/VMAT/Brachytherapy)
A good Multi-Disciplinary Team (MDT) is essential to provide the best treatment for patients of Anal cancers.

NICE CRC guidance (May 2004) advises that treatment is carried out in experienced units where cases are discussed in MDTs.

Thank you.