State-of-the-art: Standard of care for anal squamous cancer

Rob Glynne-Jones
Mount Vernon Cancer Centre
Aim to discuss

- Background
- The trials in anal cancer
- What we have learnt so far
- What is state-of-the-art
- Where do we go from here?
Aim to discuss - Chemotherapy

- Role of MMC (1 or 2 doses)
- Role of cisplatin
- Role of capecitabine
- Role of Cetuximab
Squamous cell carcinoma of the Anus

- Predominantly loco-regional disease
- Unless primary uncontrolled or recurrent
Squamous cell carcinoma of the anus

- Associated with immuno-suppression
- Organ transplantation
- Long-term cycosporin/azothiaprin etc..
- HIV infection

- Reports of tumour shrinkage when immunosuppression discontinued.
HPV

- Majority of HPV infections (HPV16 and HPV 18) are transient and subclinical and undergo subsequent clearance by the immune system.

- Persistence of infection results in development of anogenital warts as well as precancerous lesions (AIN) and finally cancers of the anogenital tract.
P16\textsuperscript{INK4A}

- In UK 90% patients mod/strongly + for p16\textsuperscript{INK4A} (Gilbert 2013)

- p16+ 37/137(27%) relapsed
- P16 - 10/16 (63%) relapsed (Gilbert 2013) p=0.0076

- Increasing evidence of inverse correlation between p16\textsuperscript{INK4A} expression (marker of HPV) and EGFR expression (on IHC)
Tumour-infiltrating lymphocyte scores stratify outcomes

- absent/low levels of TIL relapse-free rate = 63%,
- high levels of TIL = 92% (P=0.006).

Squamous cell carcinoma of the Anus

- The standard of care is chemoradiation with 5FU and MMC
SCC of Anus  Nigro et al 1983

- Preop chemoradiation to primary tumour, pelvic and inguinal nodes
- Radiotherapy  2 fields 30 Gy /15/21 days
- Chemotherapy  5FU 1000mg/m2
  Days 1-4,  29-32
- Mitomycin C 15mg/m2
  Day 1
ACT I Trial
N = 585 patients

Randomization

45Gy in 20-25 # → 15Gy Boost

45Gy in 20-25 # CRT+ 5FU /MMC → 15Gy Boost

Reassess and possibly boost after 6 weeks

Primary endpoint 3 year DFS
ACT I: Time to first local relapse

HR 0.46, p<0.001

Percentage of patients having a local relapse (%)

Time since randomisation (years)

RT alone

CMT
ESMO PRECEPTORSHIP PROGRAM

Randomised trials

- UKCCR ACT 1: CRT vs RT
- EORTC 22861: CRT vs RT
- RTOG 8704/ECOG: Role of MMC
- RTOG 98-11: Role of NACT/cisplat
dose
- ACCORD-03: Role of NACT cisplatin/ RT
- CRUK ACT 2: Role of cisplatin vs MMC
  + maintenance 5FU/cisplat
- EORTC 22011-40014: Role of 5FU vs CDDP/MMC
  not extended to phase III
### RTOG 87-04

<table>
<thead>
<tr>
<th></th>
<th>XRT+ 5 FU</th>
<th>XRT + 5 FU-MMC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>86%</td>
<td>92.2%</td>
<td></td>
</tr>
<tr>
<td>Colostomy-free survival</td>
<td>59%</td>
<td>71%</td>
<td>0.014</td>
</tr>
<tr>
<td>Colostomy rate</td>
<td>22%</td>
<td>9%</td>
<td>0.0002</td>
</tr>
<tr>
<td>DFS</td>
<td>51%</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>71%</td>
<td>78%</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Role of MMC - RTOG 8704  DFS
Options for chemotherapy

- Induction chemotherapy prior to CRT
- Different concurrent chemotherapy in CRT
- Consolidation chemotherapy after CRT
Intergroup RTOG 98-11

N = 644 patients

T2-4
N0
N+

Randomization

NACT 5FU/cisplat

45 to 59 Gy RT + 5-FU/CDDP

45 to 59 Gy + 5FU/MMC

Primary endpoint 3 year DFS
Disease Free Survival RTOG 9811

RTOG 9811  Ajani JA et al JAMA 2008
RTOG 9811 Gunderson et al 2012

Log-rank $P = .006$

HR, 1.39; 95% CI, 1.10 to 1.76

Disease-Free Survival (%)
B

Overall Survival (%)

Log-rank $P = .026$
HR, 1.37; 95% CI, 1.04 to 1.81

<table>
<thead>
<tr>
<th>Time From Random Assignment (years)</th>
<th>Failed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>87</td>
<td>325</td>
</tr>
<tr>
<td>RT + FU/MMC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>115</td>
<td>324</td>
</tr>
<tr>
<td>RT + FU/CDDP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No. at risk
RT + FU/MMC 325
RT + FU/CDDP 324

283 235 168 68
271 213 151 76
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

5 years CFS

70%
82%
77%
73%
ACCORD CFS: induction versus no induction

A

Colostomy-Free Survival (%)

Time After First Treatment (years)

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>AB</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>150</td>
<td>157</td>
</tr>
<tr>
<td>1</td>
<td>124</td>
<td>128</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>109</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>27</td>
</tr>
</tbody>
</table>

Log-rank $P = .37$

AB, induction (3-year, 79%; 5-year, 76.5%)
CD, without induction (3-year, 76%; 5-year, 75%)
ACCORD CFS: boost versus no boost

Colostomy-Free Survival (%)

- AC, boost dose of 15 Gy (3-year, 76%; 5-year, 73.7%)
- BD, boost dose of 20-25 Gy (3-year, 79%; 5-year, 77.8%)

Log-rank $P = .067$

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>AC</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>157</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>123</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>103</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>
ACT II Factorial Design
Chemoradiation Comparison

MMC 5FU CRT
No maintenance

MMC 5FU CRT
+Maintenance

versus

CisP 5FU CRT
No maintenance

CisP 5FU CRT
+Maintenance

MMC
N=472

CisP
N=468
ACT II Factorial Design
Maintenance Comparison

MMC 5FU CRT No maintenance
versus
CisP 5FU CRT No maintenance

No Maint
N=446

versus

MMC 5FU CRT Maintenance
versus
CisP 5FU CRT Maintenance

Maint
N=448
Chemoradiation Regimens

**5FU**
- Week 1: 1000mg/m² d1-4 & 29-32
- Week 2: 12mg/m² d1 only
  - iv bolus, max single dose 20 mg

**MMC**
- Week 1: 1000mg/m² d1-4 & 29-32
  - 24 hour continuous iv infusion

**CisP**
- Week 5: 60mg/m² d1 & 29
  - iv infusion
## Response at 26 weeks

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

P=0.66
## ACT II  Progression free survival

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>3-year rate, % (95%CI)</th>
<th>5-year rate , % (95% CI)</th>
<th>HR (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC</td>
<td>73 (69 to 77)</td>
<td>69 (65 to 73)</td>
<td></td>
</tr>
<tr>
<td>CisP</td>
<td>74 (69 to 77)</td>
<td>69 (64 to 73)</td>
<td>0.95 (0.75 to 1.19), p= 0.63</td>
</tr>
<tr>
<td>No-maint</td>
<td>73 (68 to 77)</td>
<td>69 (64 to 73)</td>
<td></td>
</tr>
<tr>
<td>Maint</td>
<td>74 (69 to 77)</td>
<td>70 (65 to 74)</td>
<td>0.95 (0.75 to 1.21), p=0.70</td>
</tr>
</tbody>
</table>
## Overall survival ACT II

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>3-year rate, % (95%CI)</th>
<th>5-year rate, % (95%CI)</th>
<th>HR (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC</td>
<td>84 (80 to 87)</td>
<td>79 (74 to 82)</td>
<td></td>
</tr>
<tr>
<td>CisP</td>
<td>84 (80 to 87)</td>
<td>77 (73 to 81)</td>
<td>1.05 (0.80 to 1.38), p=0.70</td>
</tr>
<tr>
<td>No-maint</td>
<td>85 (81 to 88)</td>
<td>79 (75 to 83)</td>
<td></td>
</tr>
<tr>
<td>Maint</td>
<td>83 (79 to 86)</td>
<td>76 (72 to 80)</td>
<td>1.07 (0.81 to 1.41), p=0.65</td>
</tr>
</tbody>
</table>
# Colostomy free survival in ACT II

<table>
<thead>
<tr>
<th>Comparison group</th>
<th>3-year rate, % (95% CI)</th>
<th>5-year rate , % (95% CI)</th>
<th>HR (95% CI), p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMC</td>
<td>74 (69 to 78)</td>
<td>67 (63 to 72)</td>
<td></td>
</tr>
<tr>
<td>CisP</td>
<td>73 (69 to 78)</td>
<td>67 (63 to 72)</td>
<td>1.01 (0.80 to 1.27), p=0.94</td>
</tr>
<tr>
<td>No-maint</td>
<td>67 (62 to 71)</td>
<td>65 (61 to 70)</td>
<td></td>
</tr>
<tr>
<td>Maint</td>
<td>74 (69 to 78)</td>
<td>68 (63 to 73)</td>
<td>0.88 (0.69 to 1.11), p=0.28</td>
</tr>
</tbody>
</table>
Conclusions

1. MMC/cisplatin no difference in any indicators

2. Maintenance chemotherapy no benefit
In ACT II 20 patients died of other cancers

- 3 in mitomycin group, 7 in cisplatin group
- 3 in mitomycin and maintenance group,
- 7 in cisplatin and maintenance group,

ie total 6 mitomycin CRT vs 14 platinum CRT
Squamous cell carcinoma of the Anus

- The standard of care is chemoradiation with 5FU and MMC
Question 1

- Do you need 2 doses of MMC?
  - ie 10mg/m² X 2
  - Or 12mg/m² X 1
<table>
<thead>
<tr>
<th>Trial</th>
<th>Day 1</th>
<th>Day 29</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT I</td>
<td>MMC 12mg/m2</td>
<td>none</td>
<td>MMC 12mg/m2</td>
</tr>
<tr>
<td>EORTC</td>
<td>MMC 12mg/m2</td>
<td>none</td>
<td>MMC 12mg/m2</td>
</tr>
<tr>
<td>RTOG 8704</td>
<td>MMC 10mg/m2</td>
<td>MMC 10mg/m2</td>
<td>MMC 20mg/m2</td>
</tr>
<tr>
<td>RTOG 9811</td>
<td>MMC 10mg/m2</td>
<td>MMC 10mg/m2</td>
<td>MMC 20mg/m2</td>
</tr>
<tr>
<td></td>
<td>Cisp 75mg/m2</td>
<td>Cisp 75mg/m2</td>
<td>Cisp 150mg/m2</td>
</tr>
<tr>
<td>ACCORD-03</td>
<td>Cisp 80mg/m2</td>
<td>Cisp 80mg/m2</td>
<td>Cisp 160mg/m2</td>
</tr>
<tr>
<td>ACT II</td>
<td>MMC 12mg/m2</td>
<td>none</td>
<td>MMC 12mg/m2</td>
</tr>
<tr>
<td></td>
<td>Cisp 60mg/m2</td>
<td>Cisp 60mg/m2</td>
<td>Cisp 120mg/m2</td>
</tr>
</tbody>
</table>
Comparison 1 versus 2 doses

no difference

- PFS (HR 0.85, 95% CI 0.37–1.92),
- CFS (HR 0.91, 95% CI 0.31–2.67) between the MMC1 and MMC2 groups.
- Acute grade $\geq 2$ toxicities were worse in the MMC2 group.
- 3 treatment-related deaths, all in the MMC2 group.

### ACT II: Impact of RT Compliance on PFS n=933

<table>
<thead>
<tr>
<th>Group</th>
<th>Total events</th>
<th>3 year PFS</th>
<th>Treatment adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. 50.4Gy per protocol</td>
<td>221/786 (28%)</td>
<td>76%</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>B. &lt; 40Gy</td>
<td>11/18 (61%)</td>
<td>44%</td>
<td>3.71 (2.01-6.82)</td>
<td></td>
</tr>
<tr>
<td>C. &gt;40–48.6Gy in 23-27F</td>
<td>11/21 (52%)</td>
<td>56%</td>
<td>2.26 (1.23-4.14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>D. 50.4Gy in &gt; 42 days</td>
<td>39/93 (42%)</td>
<td>62%</td>
<td>1.62 (1.15-2.28)</td>
<td></td>
</tr>
<tr>
<td>E. &gt;52Gy compensated</td>
<td>6/15 (40%)</td>
<td>59%</td>
<td>1.60 (0.7-3.61)</td>
<td></td>
</tr>
</tbody>
</table>
Impact of day 29 Chemo Compliance on PFS (n=862)

HR 1.63 (95% CI: 1.23 to 2.17) p=0.001
# Capecitabine integrated into CRT in anal cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>RT</th>
<th>MMC</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynne-Jones 2008</td>
<td>50.4 Gy in 28 fractions in 2 phases</td>
<td>Single dose of MMC 12mg/m^2 max 20mg</td>
<td>825 mg/m^2 b.i.d on radiation days</td>
</tr>
<tr>
<td>Deenen 2013</td>
<td>59.4 Gy in 33 fractions with SIB-IMRT</td>
<td>Single dose of MMC 10mg/m^2 max 15mg</td>
<td>825 mg/m^2 b.i.d on radiation days</td>
</tr>
<tr>
<td>Wan 2014</td>
<td>50-54 Gy</td>
<td>2 doses but compliance poor if Capecitabine</td>
<td>825 mg/m^2 b.i.d on radiation days</td>
</tr>
<tr>
<td>Meulendijks 2016</td>
<td>54-59 Gy</td>
<td>Single dose of MMC 10mg/m^2</td>
<td>825 mg/m^2 b.i.d on RT days</td>
</tr>
<tr>
<td>Oliveira 2016 Phase II</td>
<td>54-59 Gy</td>
<td>Single dose of MMC 15mg/m^2</td>
<td>825 mg/m^2 b.i.d on RT days</td>
</tr>
</tbody>
</table>
# Trials with Cetuximab in anal cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N of patients</th>
<th>IMRT</th>
<th>Regimen</th>
<th>Toxicity</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olivatto et al, Cancer 2013</td>
<td>21 (stopped DLT)</td>
<td>No</td>
<td>5-FU/CP + RT + cetuximab</td>
<td>High</td>
<td>OK</td>
</tr>
<tr>
<td>ACCORD 16, J Clin Oncol 2011</td>
<td>16 (stopped DLT)</td>
<td>No</td>
<td>5-FU/CP + RT + cetuximab</td>
<td>High</td>
<td>low</td>
</tr>
<tr>
<td>Norwegian Study (Johnsson)</td>
<td>Max 21 (complete)</td>
<td>Yes</td>
<td>5-FU/MMC + RT + cetuximab</td>
<td>high</td>
<td>CR 91%</td>
</tr>
</tbody>
</table>
# Trials with Cetuximab in anal cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>N of patients</th>
<th>IMRT</th>
<th>Regimen</th>
<th>Toxicity</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG3205, ASCO 2016</td>
<td>28</td>
<td>some</td>
<td>5-FU/CisP +RT + cetuximab</td>
<td>OK</td>
<td>OK 2 yr failure 5.7% (7/27)</td>
</tr>
<tr>
<td>AMC045 HIV</td>
<td>45</td>
<td>Some</td>
<td>NACT + 5-FU/CisP +RT + cetuximab</td>
<td>26% G4</td>
<td>LRF 20%</td>
</tr>
<tr>
<td>Study</td>
<td>Stage I/II/III-IV %</td>
<td>2 Year LocRegional Failure Rate</td>
<td>2 Year Overall Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------</td>
<td>---------------------------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 9811 control: MMC + 5-FU</td>
<td>47/19/31</td>
<td>25 %</td>
<td>91%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 9811*: 5-FU + Cis</td>
<td>48/17/31</td>
<td>28 %</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 3205</td>
<td>11/50/39</td>
<td>13%</td>
<td>93 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMC 045</td>
<td>24/42/34</td>
<td>7%</td>
<td>89 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IRCI anal cancer metastatic trial

InterAACT
An Open Label Phase II International Multicentre Randomized Advanced Anal Cancer Trial Comparing Cisplatin plus 5-fluorouracil (5-FU) versus Carboplatin plus Weekly Paclitaxel in Patients with Relapsed or Metastatic Disease
Clinical Protocol Version 1.0 Dated 01.02.2013
Docetaxel, cisplatin and 5-FU (DCF)

- 4/8 complete responders after only three cycles of DCF
- All the responders were HPV16 positive
- No Grade 4 toxicity observed
- Remained relapse free 19-88 months
- Option as neoadjuvant prior to primary CRT or salvage surgery

Kim S et al., Ann Oncol 2013;24: 3045-3050
Background to anti-PD-1

- **Pembrolizumab** (anti PD-1) single agent activity in metastatic setting:
  ORR -20%  SD -40% (Ott, ESMO 2015)

- **Nivolumab** (anti PD-1) single agent activity in previously treated metastatic setting:
  ORR -19%  SD – 46%, PFS 3.9 mo
  (Eng 2016 ASCO abstract 3503)
PD-L1 expression was seen in

- 33% of early stage (T1/T2) disease
- 62% of advanced /unknown stage

PD-L1-positive vs. negative patients respectively had RFS medians of 1.5 vs. 4.9 years (p = 0.068)

(Gujja ASCO abstract 2015)

Chemotherapy backbone

- Taxanes have immunogenic effects (Formenti 2003, Merritt 2003, Tsuda 2007, Golden 2014),
- Can be enhanced by checkpoint inhibition. This may be more obvious in hpv + cancers (Hawkins 1996).
- Cancer cells exposed to docetaxel, became more sensitive to the effects of cytotoxic T lymphocytes, mediated partly by calreticulin (Hodge 2013).
- Enhanced CTL lysis observed in a docetaxel-resistant cell line suggests that combining immunotherapy and chemotherapy may be effective in resistant tumours (Hodge 2013).
PLATO – PERSONALISING RADIOTHERAPY DOSE FOR ANAL CANCER

T1 N0
Anal margin

Local excision

T1, T2<4cm N0

ACT3

50.4Gy 28F
41.4Gy 23F

Standard

T2N2, T3/4 N1-3

ACT4

53.2Gy 28F
58.8Gy 28F
61.6Gy 28F

T3/4 NO

Pilot

Phase II trial

Phase II/III trial

Stratify for Cape vs. 5-FU

Ph II

Ph III

Courtesy of David Sebag-Montefiore
Thank you
MHC (major histocompatibility complex) class II molecules are a family of molecules normally found only on antigen-presenting cells such as dendritic cells, mononuclear phagocytes, some endothelial cells, thymic epithelial cells, and B cells