STANDARD OF CARE FOR ANAL CANAL SQUAMOUS CARCINOMAS

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DISCLOSURE OF INTEREST

- **Personal financial interests, honoraria for advisory role, travel grants, research grants (past 5 years):** Hoffman La-Roche, Sanofi Aventis, Amgen, Merck Serono, Servier, MSD, Array Pharmaceuticals, Bristol-Myers Squibb

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SOME STATS

• 1%–2% of digestive tract tumours and 2%–4% of colon, rectal and anal tumours.

• In Europe, ~2000 males and ~2300 females are diagnosed with anal cancer every year.

• 47.9% are diagnosed at the local stage.

• The 5-year survival for localized anal cancer is 81.7%.
RISK FACTORS

Persistent HPV infection / Previous HPV-related malignancy

Table 1. Number of cancer cases attributable to HPV and corresponding attributable fraction (AF) by cancer site, sex and age; World, 2012

<table>
<thead>
<tr>
<th>HPV-related cancer site (ICD-10 code)</th>
<th>Number of incident cases$^{1,2}$</th>
<th>Number attributable to HPV</th>
<th>AF (%)</th>
<th>Number attributable to HPV by gender</th>
<th>Number attributable to HPV by age group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>Cervix uteri (C53)</td>
<td>530,000</td>
<td>530,000</td>
<td>100.0</td>
<td>0</td>
<td>530,000</td>
</tr>
<tr>
<td>Anus$^3$ (C21)</td>
<td>40,000</td>
<td>35,000</td>
<td>88.0</td>
<td>17,000</td>
<td>18,000</td>
</tr>
<tr>
<td>Vulva$^4$ (C51)</td>
<td>34,000</td>
<td>8,500</td>
<td>24.9</td>
<td>0</td>
<td>8,500</td>
</tr>
<tr>
<td>Vagina$^3$ (C52)</td>
<td>15,000</td>
<td>12,000</td>
<td>78.0</td>
<td>0</td>
<td>12,000</td>
</tr>
<tr>
<td>Penis$^3$ (C60)</td>
<td>26,000</td>
<td>13,000</td>
<td>50.0</td>
<td>13,000</td>
<td>0</td>
</tr>
<tr>
<td>Oropharynx$^3$ (C01, C09–10)</td>
<td>96,000</td>
<td>29,000</td>
<td>30.8</td>
<td>24,000</td>
<td>5,500</td>
</tr>
<tr>
<td>Oral cavity$^3$ (C02–06)</td>
<td>200,000</td>
<td>4,400</td>
<td>2.2</td>
<td>2,900</td>
<td>1,500</td>
</tr>
<tr>
<td>Larynx (C32)</td>
<td>160,000</td>
<td>3,800</td>
<td>2.4</td>
<td>3,300</td>
<td>460</td>
</tr>
<tr>
<td>Other pharynx$^3$ (C12–C14)</td>
<td>78,000</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total HPV-related sites</td>
<td>1,200,000</td>
<td>630,000</td>
<td>54.0</td>
<td>60,000</td>
<td>570,000</td>
</tr>
</tbody>
</table>

Smoking, immunodeficiency, HIV/IADS are also associated.
PARTICULARITIES

• Mandatory histological confirmation (rule out adenocarcinoma, melanoma, GIST, NET, lymphoma).

• Anal margin tumors are generally well differentiated and often occur in men. Canal tumours are normally poorly differentiated and more common in women.

• High-grade tumours have been thought to have a worse prognosis (not confirmed in multivariate analysis).

• Basaloid, transitional, spheroidal and cloacogenic cell cancers have no additional confirmed bearing on management.

WORK UP

Table 3. Diagnostic work-up

<table>
<thead>
<tr>
<th>Mandatory</th>
<th>Optional but often recommended</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy to confirm diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full clinical body exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digital rectal examination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood tests including renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proctoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic MRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT thorax/abdomen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessment of genital tract in females for CIN/VIN</td>
<td>PET/CT</td>
<td></td>
</tr>
</tbody>
</table>

Vaginal examination to determine the site and size of the primary tumour, vaginal/vaginal septal involvement, mucosal involvement and exophytic or ulcerative tumour or the presence of a fistula.

High sensitivity in identifying involved lymph nodes and influencing RT planning by defining sites of metabolically active tumour.
**STAGING**

<table>
<thead>
<tr>
<th>Primary tumour (T)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour.</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour ≤ 2 cm in greatest dimension.</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt;2 cm but ≤ 5 cm in greatest dimension.</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour &gt;5 cm in greatest dimension.</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour of any size invades adjacent organ(s), e.g. vagina, urethra, and bladder.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph nodes (N)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis.</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in perirectal lymph node(s).</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in unilateral internal iliac and/or inguinal lymph node(s).</td>
</tr>
<tr>
<td>N3</td>
<td>Metastases in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distant metastasis (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis.</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis.</td>
</tr>
</tbody>
</table>

LOCAL AND LOCOREGIONAL DISEASE
THE BIG DIFFERENCE FROM LOWER RECTUM ADC

“Until the introduction of definitive CRT, abdomino-perineal excision (APE) was recommended for all other tumours (except those amenable to local excision). Primary APE was associated with local failure in up to half of cases, and 5-year survival rates in the region of 50%–70% were reported”

TODAY PRIMARY APE MAY BE OFFERED TO PATIENTS PREVIOUSLY IRRADIATED IN THE PELVIC REGION.

MANDATORY MULTIDISCIPLINARY APPROACH

• Achieve cure with locoregional control and preservation of anal function (QOL),

• 5FU-based CRT and other cytotoxic agents (mainly MMC) have been established as SOC, leading to complete tumour regression in 80%-90%.

• The role of surgery as a salvage treatment is accepted.

• Assessment and treatment should be carried out in specialised centres
• Recommendations are based on the results of the phase II and six randomised phase III trials
• 5-FU with MMC combined with radiotherapy are generally recommended, rather than 5-FU and cisplatin, MMC and cisplatin, any single drug or any combination of three drugs [I, A].

Concomitant Radiotherapy and Chemotherapy Is Superior to Radiotherapy Alone in the Treatment of Locally Advanced Anal Cancer: Results of a Phase III Randomized Trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups

By H. Bartelink, F. Roelofsen, F. Eschwege, P. Rougier, J.F. Bosset, D. Gonzalez Gonzalez, D. Peiffert, M. van Glabbeke, and M. Pierart

J Clin Oncol 1997

Role of Mitomycin in Combination With Fluorouracil and Radiotherapy, and of Salvage Chemoradiation in the Definitive Nonsurgical Treatment of Epidermoid Carcinoma of the Anal Canal: Results of a Phase III Randomized Intergroup Study

By Marshall Flam, Madhu John, Thomas F. Pajak, Nicholas Petrelli, Robert Myerson, Scotte Doggett, Jeanne Quivey, Marvin Rotman, Herbert Kerman, Lawrence Coia, and Kevin Murray


Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I)

Northover et al. Eur J Cancer 2010
ROLE OF ASSESSMENT OF RESPONSE

- Anal cancers tend to regress slowly after completion of CRT treatment.
- Digital rectal evaluation is the mainstay of determining complete response after treatment (absence of tumour and/or ulceration).
- Biopsies of persistent clinically suspicious lesions 8–12 weeks after CRT completion are not routinely recommended (treatment-related effects may confound pathological interpretation).

- Assessment at 26 weeks is the most discriminating end point with the most significant effect on outcome, and is therefore the optimum time point for definitive assessment with a view to salvage surgery.
- Residual or ‘recurrent’ tumor must be confirmed histologically before considering proceeding to radical surgery.

5FU 1000 mg/m² days 1–4 (week 1) and 29–32 (week 5) by continuous 24 h IV infusion. • MITOMYCIN 12 mg/m² IV bolus on day 1 (maximum single dose 20 mg). • RADIOTHERAPY*: Total dose 50.4 Gy delivered in 28 daily fractions starting on Day 1.
FEASIBILITY OF CAPECITABINE/MMC

Although randomised trials have not been carried out, the evidence from phase II studies and data extrapolated from randomised trials in rectal cancer suggest that capecitabine might be considered as an alternative to infused 5-FU.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligible patients</th>
<th>Study design</th>
<th>Treatments</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTRA study</td>
<td>Any stage, n=31</td>
<td>Phase II</td>
<td>CRT (MMC-Cape)</td>
<td>4-wk CR: 77% 6-m LRC: 90%</td>
</tr>
<tr>
<td>Oliveira et al</td>
<td>T2-4,N0 or Tany,N+</td>
<td>Phase II</td>
<td>CRT (MMC-Cape)</td>
<td>6-m LRC: 86%</td>
</tr>
<tr>
<td>Goodman et al</td>
<td>Stage I-III, n=107</td>
<td>Retrospective</td>
<td>CRT (MMC-5FU) CRT (MMC-Cape)</td>
<td>2-yr LRR: 6.5% 2-yr OS: 87%</td>
</tr>
<tr>
<td>Meulendiks et al</td>
<td>T2-4,N0-1 or T1-4,N2-3</td>
<td>Retrospective</td>
<td>CRT (MMC-5FU) CRT (MMC-Cape)</td>
<td>3-yr LRC: 76% 3-yr OS: 78%</td>
</tr>
</tbody>
</table>


Table presented by Francesco Scafani at ESMO CRC preceptorship May 2019, Valencia
OTHER STRATEGIES EXPLORED

• Based on the role of cisplatin instead of MMC investigating also neo-adjuvant or maintenance treatment

• Key messages:
  • Cisplatin in combination with infused 5-FU and radiation does not improve either complete RR or local control compared with MMC and does not reduce overall toxicity (less myelotoxicity);
  • Neo-adjuvant chemotherapy before CRT has not improved either locoregional or distant control, and colostomy-free survival (CFS) is significantly worse
  • Additional maintenance/consolidation chemotherapy following CRT has not impacted on local control, DFS or OS

METASTATIC DISEASE
METASTATIC DISEASE

• Approximately 10%–20% of patients suffer distant relapse

• The most common sites of metastatic spread are to the para-aortic nodes, liver, lungs and skin, which usually appear relatively late and in the context of local persistence or recurrence of disease following treatment.

• The prognosis in this group is poor with only 10% of patients with distant metastases surviving 2 years or more

• Patients with small volume or isolated metastatic disease should be further discussed by an appropriate MDT, in case there are surgical or CRT options.
INTERAACT TRIAL

A multicentre open label randomised phase II advanced anal cancer trial of CDDP - 5-FU vs carboplatin plus weekly paclitaxel in patients with inoperable locally recurrent or metastatic treatment naïve disease - An International Rare Cancers Initiative trial

Inoperable locally recurrent or metastatic anal cancer ECOG PS 0-2

197 pts 2013 to 2017

- Cisplatin 60 mg/m² d1 q21
- 5FU 1000 mg/m² d1-4 q21
- Carboplatin AUC5 d1 q28
- Paclitaxel 80 mg/m² d1,8,15 q28

Rao et al. LBA21, ESMO 2018
EPITOPES-HPV02 TRIAL

Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): a multicentre, single-arm, phase 2 study

- Inoperable locally recurrent/metastatic disease, ECOG PS 0-1 (66 pts included)
- PFS at 12 months
- Chemotherapy regimens (investigator’s choice):
  - Standard DCF: docetaxel 75 mg/m2 & cisplatin 75 mg/m2 on day 1 and 5-FU 750 mg/m2 per day for 5 days, every 3 wks
  - Modified DCF x8: docetaxel 40 mg/m2 & cisplatin 40 mg/m2 on day 1 and 5-FU 1200 mg/m2 per day for 2 days, every 2 wks
- PFS rate (12 m): 47%, 1y OS 83%, ORR 89%

Kim et al. Lancet Oncol 2018
ROLE OF CHECKPOINT INHIBITORS

HPV+ anal cancers may confer an immunogenic microenvironment

Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study

Kim et al. Lancet Oncol 2018

ORR: 24%, 5.8 months (DR, 72%), mOS 11.5 months

Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal

Ott et al. Ann Oncol 2017

ORR: 17%, mPFS: 3.0 months, mOS: 9.3 months

Graphs showing survival and response rates.
ASCC PROFILING

Comprehensive genomic profiling of anal squamous cell carcinoma reveals distinct genomically defined classes

- Comprehensive genomic profiling of 70 ASCC patients. Recurrent alterations in PI3K/AKT/mTOR pathway genes were observed commonly.
- Recurrent genomic alterations ($n \geq 2$) and differences between HPV(+) and HPV(−) cases of ASCC
SUMMARY AND CONCLUSIONS

• An multidisciplinary approach is essential for the optimal management of anal cancer.

• Despite the results of four randomised phase III trials in anal cancer, the paradigm of external beam radiation therapy with concurrent 5-FU and MMC developed over 30 years ago by Norman Nigro remains the standard of care.

• As anal cancer is a rare tumour, it is in the interest of all patients to be offered participation in a clinical trial.

• Carboplatin-paclitaxel may constitute a new option for this population

• Immunotherapy could play a role in this entity

• Biological particularities may have an impact in outcomes
THANK YOU!

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