# TREATMENT RELATED MORBIDITIES AND THEIR MANAGEMENT IN CARCINOMA CERVIX

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# INTRODUCTION

- Cervical cancer is a world-wide health problem,
- Higher incidence among women in low socioeconomic classes,
- Higher prevalence of human papilloma virus, which is the
- In several developed countries, population screening and improved hygiene have lowered mortality rates for cervical cancer

  ( Laara E, et al, Lancet 1987)
- The choice of treatment for cervical cancer depends on the stage of the tumour.

# INTRODUCTION

- For the smaller tumours confined to the cervix (stages IA and IB1) the treatment consists of surgery or radiotherapy/CRT, with 5-year survival rates of 80% to 95%.

- For the more advanced disease (stage IB2–IVA) the 5- years survival is less favourable with radiotherapy as the sole modality. Therefore many attempts have been made over the last decades to improve the treatment outcome in this group.

# INTRODUCTION

- The tolerance of the normal tissues in the pelvis was a major barrier for radiotherapy and combinations with chemotherapy.

- Since Feb 1999, five randomized trials have studied the addition of chemotherapy to radiotherapy and showed better local control and survival for the combination CRT.

(Keys HM, Peters, Morris M, Rose PG, Whitney CW, 1999, NCI Alert)

# INTRODUCTION

- The positive results of the other studies were supported by a meta analysis, which showed an overall survival benefit of 12%.

**(Green JA, Lancet 2001)**

- A Cochrane review published in 2002 concluded that concomitant chemotherapy and radiotherapy appears to improve progression-free survival and overall survival in locally advanced disease.

**(Green J, Oxford 2002)**

- However, the reviewers also stated that there was only sparse data available on long-term side effects.

- With this benefit in overall survival in mind, it will be relevant to acknowledge the acute and long-term toxicity of these combined treatment modalities.

# TOXICITY SCORING

- The absence of a uniform classification system for reporting treatment morbidity has resulted in a considerable inconsistency in the reporting of treatment complications in cervical cancer patients.

Reviewed toxicity of the RT and surgical Rx of cervical cancer (1938 – 1986)
From the 96 articles reviewed 30 used a defined scale
**22** different classifications

(SISMONDI P, RADIOTHER ONCOL 1989)

# HISTORY

## CHASSAGNE GLOSSARY (1980)

- It describes morbidity in cervical cancer patients treated with radiotherapy.
- Combines subjective and objective symptoms and signs.
- Specifies whether symptomatic therapy is necessary.
- Complications are divided into three grades of severity.
- Do not discriminate between early and late occurrence and between temporary or lasting symptoms.

(Chassagne D. Bull Cancer Paris 1980)

# HISTORY....

## FRANCO-ITALIAN GLOSSARY (FIG) (1987)

- In this scoring system it was divided into four grades for each affected organ.
- Each grade is further subdivided into a maximum of six subgroups.
- A subgroup includes several signs and symptoms.

(Chassagne D, Radiother Oncol 1993)

- 1998 SHAKESPEARE ET AL, reviewed papers using the revised FIG system. The authors concluded that more than half of all toxicities could not be accurately graded because it did not account for all complications nor allow grading of subjective assessments.

(Shakespeare TP, Int J Gynecol Cancer 1998)

# HISTORY....

- Pederson et al, criticised the FIG because of the information loss when a specific grading was used, and introduced the Danish AADK scoring system.
- This system allows the registration of early and late morbidity, the type of complication and its first date of appearance.

- The system scores the baseline incidence and the actuarial estimation of complications.
- Early morbidity was defined as a complication occurring within 3 months after radiotherapy and late morbidity as a complication diagnosed after that period.

- Complications were graded as mild, moderate and severe.

**(Pedersen D, et al, Radiother Oncol 1993)**

# HISTORY....

- In **1995** the international collaboration between the RTOG and the EORTC resulted in the recommendation of the SOMA/LENT toxicity score.
- There was a general agreement that Late Effects of Normal Tissue (LENT) toxicity should include five grades:

- Grade 1 represents minor symptoms requiring no treatment,
- Grade 2 moderate symptoms requiring only conservative treatment,
- Grade 3 severe symptoms requiring more aggressive treatment
- Grade 4 irreversible damage requiring major therapeutic intervention.
- Grade 5 indicates fatality or loss of an organ or structure.

**(Rubin P,IJROBP.1995)**

# HISTORY....

- After the agreement on the SOMA/LENT scoring system in 1995 it has been suggested that a trial period should precede the validation and final recommendations.
- The SOMA/LENT scoring system has not yet been officially validated.
- Nowadays the classifications most used are the:
  - RTOG/EORTC,
  - LENT/SOMA,
  - European,
  - WHO,
  - French/Italian,
  - AADK and the
  - Common Toxicity Criteria (CTC).

- The CTCAE 3.0 grading is currently endorsed by a number of large organizations such as the EORTC, NCI and RTOG.

An advantage of the CTC grading system is the fact that it covers the toxicity caused by radiotherapy as well as chemotherapy

- For the late radiation toxicity the RTOG/EORTC late toxicity criteria are available for all major organs and is more frequently used.

(Cox JD, IJROBP,1995)

Despite many efforts, a single scoring system for early and late morbidity has not yet been adopted.

# TYPES OF TOXICITIES

Toxicity due to radiation and chemotherapy can be grouped into either:

1. Acute toxicity: currently defined as toxicity which occurs during or up to 90 days after radiotherapy.
2. Late toxicity: defined as any toxicity which occurs ≥ 3 months.

- The distinction between acute and late toxicity is based on the $\infty/\beta$ ratio of the linear-quadratic model.

This assumption suggests that late toxicity is due to different pathophysiologic mechanisms to those associated with acute toxicity.

# SCORING SYSTEMS

**TABLE I** Scoring systems used for treatment complications of (chemo) radiotherapy for cervical cancer

| System | Basic features | Limitations | Reference number (year of publication) |
|---|---|---|---|
| WHO | Derived from a system used in medical oncology | Focuses on early reactions; not well suited for radiotherapy | (158) (1981) |
| European | Focuses on end-points rather than organs; attempts to break down scores in specific symptoms, thus allowing retrospective re scoring of grades | Based on previously published systems; still under evaluation | (159) (1989) |
| French/Italian Glossary (FIG) | Aimed at treatments for gynaecological cancer; also suitable for surgical complications | Mixes various end-points for the same organ | (31) (1993) |
| AADK | Aimed at treatments for gynaecological cancer | Mainly based on medical interventions to relieve treatment-related morbidity | (27) (1993) |
| LENT/SOMA | Very comprehensive; scores subjective symptoms, objective signs, and laboratory test results | Not clear how various expressions of damage should be combined into a single grade; needs validation | (33,34) (1995) |
| RTOG/EORTC | Very comprehensive; available for all major organs that may be injured by radiotherapy; proved to be feasible | Mixes various end-points for the same organ | (37) (1995) |
| CTC version 2.0 | Very comprehensive; more than 260 individual adverse events. Dynamic document. Applicable to multiple modalities. | Focuses on acute reactions. Lengthy document | (36) (2000) |

# NCI CTCAE V3.0

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# GRADING OF CHEMO-RADIATION TOXICITY NCI CTC V3.0

| Toxicity | Grade 0 | Grade I | Grade II | Grade III | Grade IV |
|---|---|---|---|---|---|
| **Nausea** | None. | Able to eat, reasonable intake. | Intake significantly decreased but can eat. | No significant intake. | -- |
| **Vomiting** | None. | 1 episode in a day. | 2-5 in a day. | 6-10 in day. | >10 in a day or requiring parenteral support. |
| **Diarrhea** | None. | Increase of 2-3 stools per day over pretreatment. | Increase of 4-6 stools/day or nocturnal stools or moderate cramping. | Increase of 7-9 stools/day or incontinence or severe cramping. | Increase of >10 stools/day or grossly bloody diarrhea or need for parenteral support. |

# GRADING OF CHEMO-RADIATION TOXICITY NCI CTC V3.0

| | | | | | |
|---|---|---|---|---|---|
| **Hematuria** | Nil. | Microscopic. | Gross, no clots. | Gross plus clots. | Requires transfusion. |
| **Neuro-hearing** | None. | Asymptomatic. Hearing loss on audiometry only. | Tinnitus. | Hearing loss interfering with function but correctable with hearing aid. | Deafness not correctable. |
| **Skin** | None | Scattered macular or papular eruptions or erythema that is asymptomatic. | Scattered macular or papular eruptions or erythema with pruritis or other associated symptoms. | Generalised symptomatic macular, papular or vesicular eruptions. | |

# GRADING OF CHEMO-RADIATION TOXICITY NCI CTC V3.0

| Toxicity | Grade 0 | Grade I | Grade II | Grade III | Grade IV |
|---|---|---|---|---|---|
| **Hemoglobin (gm%** | Normal | < LLN – 10.0 | < 10.0 – 8.0 | < 8.0 - 6.5 | < 6.5 |
| **Leucocytes (Total WBC/mm$^3$)** | Normal | < LLN - 3000 | < 3000 - 2000 | < 2000 - 1000 | < 1000 |
| **Platelet Count/mm$^3$** | Normal | < LLN – 75,000 | < 75,000 – 50,000 | < 50,000 – 25,000 | < 25,000 |

# RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEMA

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# RTOG/EORTC LATE RADIATION MORBIDITY SCORING SCHEMA

| Organ – Tissue | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|---|
| **Skin** | None. | Slight atrophy. Pigmentation change. | Patch atrophy. Moderate telangiectasia. Total hair loss. | Marked atrophy. Gross telangiectasia. | Ulceration. | Death directly related to radiation late effects. |
| **Subcutaneous tissues** | None. | Slight induration (fibrosis) and loss of subcutaneous fat. | Moderate fibrosis but asymptomatic. Slight field contracture <10% linear reduction. | Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement. | Necrosis. | |
| **Mucous membrane** | None. | Slight atrophy and dryness. | Moderate atrophy and telangiectasia. Little mucus. | Marked atrophy with complete dryness. Severe telangiectasia. | Ulceration. | |

# RTOG/EORTC Late Radiation Morbidity Scoring Schema

| | | | | | | |
|---|---|---|---|---|---|---|
| **Small/large intestine** | None. | Mild diarrhea, mild cramping. Bowel movements 5 times daily. Slight rectal bleeding or discharge. | Moderate diarrhea and colic. Bowel movements > 5 times daily. Excessive rectal mucus or intermittent bleeding. | Obstruction or bleeding requiring surgery. | Necrosis. Perforation Fistula. | |
| **Bladder** | None. | Slight epithelial atrophy. Minor telangiectasia (microscopic hematuria). | Moderate frequency. Generalized telangiectasia. Intermittent macroscopic hematuria. | Severe frequency and dysuria. Severe generalized telangiectasia (often with petechiae). Frequent hematuria. Reduction in bladder capacity <150cc. | Necrosis/ contracted bladder (capacity <100cc) /severe haemorr-hagic cystitis. | |

# LENT/SOMA SCALE FOR LONG TERM TOXICITY

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# SMALL INTESTINE / COLON

| | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| **S**ubjective | | | | |
| Stool frequency | 2 - 4 per day | 5 - 8 per day | > 8 per day | Refractory diarrhea |
| Stool consistency | Bulky | Loose | Mucous, dark, watery | |
| Pain | Occasional & minimal | Intermittent & tolerable | Persistent & intense | Refractory / Rebound |
| Constipation | 3 - 4 per week | Only 2 per week | Only 1 per week | No stool in 10 days |
| **O**bjective | | | | |
| Melena | Occult / Occasional | Intermittent & tolerable, normal hemoglobin | Persistent, 10% - 20% decrease in hemoglobin | Refractory or frank blood, >20% decrease in hemoglobin |
| Weight loss from time of treatment | ≥ 5% - 10% | > 10% - 20% | > 20% - 30% | > 30% |
| Stricture | > 2/3 normal diameter with dilatation | 1/3 - 2/3 normal diameter with dilatation | < 1/3 normal diameter | Complete obstruction |
| Ulceration | Superficial ≤ 1 $cm^2$ | Superficial > 1 $cm^2$ | Deep ulcer | Perforation, fistulae |
| **M**anagement | | | | |
| Pain | Occasional non-narcotic | Regular non-narcotic | Regular narcotic | Surgical intervention |
| Stool consistency / frequency | Diet modification | Regular use of non-narcotic antidiarrheal | Continuous use of narcotic antidiarrheal | |
| Bleeding | Iron therapy | Occasional transfusion | Frequent transfusions | Surgical intervention |
| Stricture | Occasional diet adaptation | Diet adaptation required | Medical intervention, NG suction | Surgical intervention |
| Ulceration | | | Medical intervention | Surgical intervention |

| | |
|---|---|
| **A**nalytic | |
| CT | Assessment of wall thickness, sinus and fistula formation |
| MRI | Assessment of wall thickness, sinus and fistula formation |
| Absorption studies | Assessment of protein and fat absorption and metabolic balance |
| Barium radiograph | Assessment of lumen and peristalsis |

# RECTUM

| | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| **Subjective** | | | | |
| Tenesmus | Occasional urgency | Intermittent urgency | Persistent urgency | Refractory |
| Mucosal loss, | Occasional | Intermittent | Persistent | Refractory |
| Sphincter control | Occasional | Intermittent | Persistent | Refractory |
| Stool frequency | 2 - 4 per day | 4 - 8 per day | > 8 per day | Uncontrolled diarrhea |
| Pain | Occasional & minimal | Intermittent & tolerable | Persistent & intense | Refractory & excruciating |
| **Objective** | | | | |
| Bleeding | Occult | Occasionally > 2/week | Persistent/daily | Gross hemorrhage |
| Ulceration | Superficial ≤ 1 $cm^2$ | Superficial > 1 $cm^2$ | Deep ulcer | Perforation, Fistulae |
| Stricture | > 2/3 normal diameter with dilatation | 1/3 - 2/3 normal diameter with dilatation | < 1/3 normal diameter | Complete obstruction |
| **Management** | | | | |
| Tenesmus & stool frequency | Occasional, ≤ 2 antidiarrheals/week | Regular, > 2 antidiarrheals/week | Multiple, > 2 antidiarrheals/day | Surgical intervention/ Permanent colostomy |
| Pain | Occasional non-narcotic | Regular non-narcotic | Regular narcotic | Surgical intervention |
| Bleeding | Stool softener, iron therapy | Occasional transfusion | Frequent transfusions | Surgical intervention / Permanent colostomy |
| Ulceration | Diet modification, stool softener | Occasional steroids | Steroids per enema, hyperbaric oxygen | Surgical intervention/ Permanent colostomy |
| Stricture | Diet modification | Occasional dilatation | Regular dilatation | Surgical intervention/ Permanent colostomy |
| Sphincter control | Occasional use of incontinence pads | Intermittent use of incontinence pads | Persistent use of incontinence pads | Surgical intervention/ Permanent colostomy |

| | |
|---|---|
| **Analytic** | |
| Barium enema | Assessment of lumen and peristalsis |
| Proctoscopy | Assessment of lumen and mucosal surface |
| CT | Assessment of wall thickness, sinus and fistula formation |
| MRI | Assessment of wall thickness, sinus and fistula formation |
| Anal manometry | Assessment rectal compliance |
| Ultrasound | Assessment of wall thickness, sinus and fistula formation |

# BLADDER / URETHRA

| | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| **Subjective** | | | | |
| Dysuria | Occasional & minimal | Intermittent & tolerable | Persistent & intense | Refractory & excruciating |
| Frequency | 3 - 4 hour intervals | 2 - 3 hour intervals | 1 - 2 hour intervals | Hourly |
| Hematuria | Occasional | Intermittent | Persistent with clot | Refractory |
| Incontinence | < weekly episodes | < daily episodes | ≤2pads/undergarments/day | Refractory |
| Decreased stream | Occasionally weak | Intermittent | Persistent but incomplete obstruction | Complete obstruction |
| **Objective** | | | | |
| Hematuria | Microscopic, normal hemoglobin | Intermittent macroscopic, < 10% decrease in hemoglobin | Persistent macroscopic, 10% 20% decrease in hemoglobin | Refractory, > 20% decrease in hemoglobin |
| Endoscopy | Patchy atrophy or Telangiectasia without bleeding | Confluent atrophy or Telangiectasia with gross bleeding | Ulcerations into muscle | Perforation, fistula |
| Maximum volume | > 300 cc - 400 cc | > 200 cc - 300 cc | > 100 cc - 200 cc | ≤ 100 cc |
| Residual volume | 25 cc | > 25 cc - 100 cc | > 100 cc | |
| **Management** | | | | |
| Dysuria | Occasional non-narcotic | Regular non-narcotic | Regular narcotic | Surgical intervention |
| Frequency | Alkalization | Occasional anti-spasmodic | Regular narcotic | Cystectomy |
| Hematuria/ Telangiectasia | Iron therapy | Occasional transfusion or single cauterization | Frequent transfusion or coagulation | Surgical intervention |
| Incontinence | Occasional use of incontinence pads | Intermittent use of incontinence pads | Regular use of pad or self-catheterization | Permanent catheter |
| Decreased stream | | < Once-a-day self-catheterization | Dilatation, > once-a-day self-catheterization | Permanent catheter, surgical intervention |
| **Analytic** | | | | |
| Cystography | Assessment of mucosal surface | | | |
| Volumetric analysis | Assessment of bladder capacity in milliliters | | | |
| Contrast radiography | Assessment for ulcers, capacity and contractility | | | |
| Ultrasound | Assessment of wall thickness, sinus and fistula formation | | | |
| Electromyography | Assessment of sphincter activity using intralumenal pressure transducer, contraction pressure and volume curves | | | |

# VAGINA

| | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| **Subjective** | | | | |
| Dyspareunia | Occasional & minimal | Intermittent & tolerable | Persistent & intense | Refractory & excruciating |
| Dryness | Occasional | Intermittent | Persistent | Refractory |
| Bleeding | Occasional | Intermittent | Persistent | Refractory |
| Pain | Occasional & minimal | Intermittent & tolerable | Persistent & intense | Refractory & excruciating |
| **Objective** | | | | |
| Stenosis / length | > 2/3 normal length | 1/3 - 2/3 normal length | < 1/3 normal length | Obliteration |
| Dryness | Asymptomatic | Symptomatic | Secondary dysfunction | |
| Ulceration / necrosis | Superficial, ≤ 1 $cm^2$ | Superficial, > 1 $cm^2$ | Deep ulcer | Fistulae |
| Atrophy | Patchy | Confluent | Nonconfluent | Diffuse |
| Appearance | Telangiectasia without bleeding | Telangiectasia with gross bleeding | | |
| Synechiae | | Partial | Complete | |
| Bleeding | | On contact | Intermittent | Persistent |
| **Management** | | | | |
| Dyspareunia/ Pain | Occasional non-narcotic | Regular non-narcotic | Regular narcotic | Surgical intervention |
| Atrophy | Occasional hormone cream | Intermittent hormone cream | Regular hormone cream | |
| Bleeding | Iron therapy | Occasional transfusion | Frequent transfusions | Surgical intervention |
| Stenosis | Occasional dilation | Intermittent dilation | Persistent dilation | Surgical reconstruction |
| Dryness | Hormone replacement | Artificial lubrication | | |
| Ulceration | Conservative | Debridement | $HBO_2$ | Graft, Surgical repair |
| **Analytic** | | | | |
| MRI | Assessment of wall thickness, sinus and fistula formation | | | |
| Ultrasound | Assessment of wall thickness, sinus and fistula formation | | | |
| EUA<br>Cytology / biopsy | Assessment of wall diameter and length and mucosal surface | | | |

# SKIN / SUBCUTANEOUS TISSUE

| | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
|---|---|---|---|---|
| **Subjective** | | | | |
| Scaliness/Roughness | Present / asymptomatic | Symptomatic | Require constant attention | |
| Sensation | Hypersensitivity, pruritus | Intermittent pain | Persistent pain | Debilitating dysfunction |
| **Objective** | | | | |
| Edema | Present / asymptomatic | Symptomatic | Secondary dysfunction | Total dysfunction |
| Alopecia (scalp) | Thinning | Patchy, permanent | Complete, permanent | |
| Pigmentation change | Transitory, slight | Permanent, marked | | |
| Ulcer / Necrosis | Epidermal only | Dermal | Subcutaneous | Bone exposed |
| Telangiectasia | Minor | Moderate < 50% | Gross ≥ 50% | |
| Fibrosis / Scar | Present / asymptomatic | Symptomatic | Secondary dysfunction | Total dysfunction |
| Atrophy / Contraction (depression) | Present / asymptomatic | Symptomatic / < 10% | Secondary dysfunction / 10% - 30% | Total dysfunction / > 30% |
| **Management** | | | | |
| Dryness | | | Medical intervention | |
| Sensation | | Intermittent medical intervention | Continuous medical intervention | |
| Ulcer | | | Medical intervention | Surgical intervention/ amputation |
| Edema | | | Medical intervention | Surgical intervention/ amputation |
| Fibrosis / Scar | | | Medical intervention | Surgical intervention/ amputation |
| **Analytic** | | | | |
| Color photographs | Assessment of changes in appearance | | | |

# RESULTS OF TOXICITY

# ACUTE TOXICITY (RT ONLY)

- The treatment morbidity in **442 patients**, who received radiotherapy for cervical cancer between ***1974 and 1984***, was retrospectively studied.

- Most frequently seen (61%) in the recto-sigmoid.
- urinary bladder in 27%.
- Local dermal toxicity in 20%.
- Gynecological morbidity in 12%.
- Early morbidity required medication in 68% and hospitalisation in 10% of the patients.
- Severe early morbidity was observed in 2% of the patients.

**( Pederson et al; IJROBP,1994)**

# RT ALONE RESULTS

**TABLE 2** Moderate and severe acute toxicity of single modality radiotherapy

| Reference | RT (19) | RT + Hysterectomy (18) | Hysterectomy + RT (22) | RT (23) | RT (58) | RT (149) |
|---|---|---|---|---|---|---|
| Patients (*n*) | 193 | 186 | 116 | 126 | 398 | 25 |
| Toxicity (any grade) | | | | | | |
| Hematological NOS* (%) | 1 | 2 | – | 0 | – | – |
| Thrombocytopenia (%) | – | – | 0 | – | – | 0 |
| Leukopenia (%) | – | – | 1 | – | – | 0 |
| Anemia (%) | – | – | 0 | – | – | 0 |
| Genitourinary (%) | 0 | 3 | – | 1 | 1 | 4 |
| Renal failure (%) | – | – | 0 | – | – | – |
| Cutaneous (%) | 1 | 2 | 0 | 0 | 5 | – |
| Neurological (%) | – | 1 | – | 0 | – | 0 |
| Gastrointestinal* (%) | – | 5 | – | 1 | 7 | – |
| Diarrhoea (%) | – | – | 6 | – | – | – |
| Nausea and vomiting (%) | 1 | – | – | – | – | – |
| Nausea (%) | – | – | 2 | – | – | – |
| Vomiting (%) | – | – | 2 | – | – | – |
| Abdominal pain (%) | – | – | 2 | – | – | – |
| Bowel and rectal abnormalities (%) | 1 | – | 1 | – | – | 4 |

shows that acute radiotherapy induced toxicity is mainly gastrointestinal

# ACUTE TOXICITY (CHEMO-RT)

- The most frequently used drugs in cervical cancer trials for chemo-radiation have been hydroxyurea, cisplatin, carboplatin, 5-FU.
- Comparing the various studies is difficult because of the differences in the chemotherapeutic regimens, the radiotherapy delivered and whether or not an surgery was performed.
- The main toxicity encountered during combined chemo-radiation is haematological and gastro-intestinal.

# CHEMO-RT RESULTS

**TABLE 4** Moderate and severe acute toxicity of combined modality treatment

| Reference | RT + Cis +5-FU (19)[c] | RT + Cis + Hysterectomy (18)[c] | Hysterectomy RT +/– Cis +5-FU (22)[c] | RT +/– Cis (23)[c] | RT +/– HU Cis + 5-FU (21)[c] | | RT +/– HU RT +/– Cis RT +/– Cis +5-FU (20)[c] | | | RT +/– 1×/week Cis RT +/– 2×/week Cis (149)[c] | | Split course hyper fractionated RT + Cis +5-FU (150)[b] | RT + Cis (14)[b] | RT + 5-FU + mitomycin C + Cis (151)[b] | RT + Cis (10)[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients (*n*) | 195 | 183 | 122 | 127 | 188 | 169 | 177 | 176 | 173 | 22 | 17 | 29 | 55 | 36 | 60 |
| Toxicity | | | | | | | | | | | | | | | |
| Hematological[a] (%) | 37 | 21 | – | 5 | – | – | – | – | – | 9 | 29 | – | – | – | – |
| Thrombocytopenia (%) | – | – | 1 | – | 1 | 0 | 1 | 1 | 2 | 0 | 0 | 0 | 0 | 11 | 2 |
| Leukopenia (%) | – | – | 35 | – | 24 | 4 | 12 | 13 | 27 | 18 | 47 | 24 | 8 | 33 | – |
| Anemia (%) | – | – | 3 | – | – | – | – | – | – | – | – | – | – | – | 3 |
| Granulocytopenia (%) | – | – | – | – | – | – | – | – | – | – | – | – | – | – | 10 |
| Genitourinary (%) | 1 | 2 | – | 2 | 2 | 1 | 2 | 3 | 1 | – | – | – | – | 3 | 0 |
| Renal failure (%) | – | – | 1 | – | – | – | – | – | – | – | – | – | 0 | – | – |
| Cutaneous (%) | 3 | 0 | 2 | 2 | 2 | 2 | 2 | 1 | 3 | 0 | 0 | – | – | – | 2 |
| Neurological (%) | – | 1 | – | 2 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | – | 0 | – | 0 |
| Gastrointestinal[a] (%) | – | 14 | – | 13 | 4 | 8 | 8 | 7 | 10 | – | – | – | 0 | – | – |
| Diarrhoea (%) | – | – | 10 | – | – | – | – | – | – | 0 | 0 | 0 | – | 8 | 5 |
| Nausea and vomiting (%) | 9 | – | – | – | – | – | – | – | – | 0 | 0 | – | – | 0 | 0 |
| Nausea (%) | – | – | 14 | – | – | – | – | – | – | – | – | 0 | – | – | – |
| Vomiting (%) | – | – | 12 | – | – | – | – | – | – | – | – | – | – | – | – |
| Abdominal pain (%) | – | – | – | – | – | – | 0 | 0 | 1 | – | – | – | – | – | – |
| Bowel and rectal abnormalities (%) | 9 | – | 2 | – | – | – | – | – | – | 5 | 12 | – | – | – | – |

[a] Not otherwise specified, Cis = cisplatin, HU = hydroxyurea, 5-FU = 5-fluorouracil, RT = radiotherapy.

[b] Phase II study.

[c] Phase III study.

Acute toxicity grades for each trial specified in standard versus chemoradiation status

| | Chemoradiation | | | | Radiotherapy | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 and 2 | | 3 and 4 | | 1 and 2 | | 3 and 4 | |
| | Number | % | Number | % | Number | % | Number | % |
| Haemoglobin [21,28,32,42,44,45] | 448/1141 | 39.3 | 78/1201 | 6.5 | 231/796 | 29.0 | 35/858 | 4.1 |
| WCC [15,21,28,31,32,42,44,45] | 656/1328 | 49.4 | 227/1388 | 16.4 | 393/982 | 40 | 82/1044 | 7.9 |
| Platelets [15,21,28,31,32,42,44,45] | 251/1223 | 20.5 | 22/1283 | 1.7 | 87/874 | 10 | 4/936 | 0.4 |
| Haematology' NOS [17,20,23] | 104/195 | 53.3 | 112/378 | 27.6 | 34/198 | 17.2 | 5/379 | 1.3 |
| Genitourinary [17,23,28,32,42] | 198/1133 | 17.5 | 21/1358 | 1.5 | 165/966 | 17.1 | 19/1191 | 1.6 |
| Gastrointestinal [17,23,28,32,42] | 530/1172 | 45.2 | 112/1397 | 8 | 404/991 | 40.8 | 51/1216 | 4.2 |
| Neurological [23,28,32,42] | 52/836 | 6.2 | 5/836 | 0.6 | 18/670 | 2.7 | 3/670 | 0.5 |
| Skin [17,23,28,32,42] | 161/1028 | 15.7 | 23/1223 | 1.9 | 113/858 | 13.2 | 13/1051 | 1.2 |

# LATE TOXICITY

# LATE TOXICITY

- Historical data report a 5% chance of developing late pelvic complications following curative intra-cavitary and EBRT.

- A study in 1,383 patients treated with radiotherapy between 1970 and 1981 with a minimum follow-up of 5 years, showed that **14.5%** of the patients treated before **1980** experienced severe complications (using a three grade scale) compared to only **3.5%** in the period after 1980 (when the treatment protocol was changed from **AP-PA fields** into a **four-field box technique**), without any difference in local recurrence.

  **(Horiot JC, IJROBP; 1988)**

- Eifel et al. reported late complications in 1784 patients treated with radiotherapy for FIGO stage IB between 1960 and 1989. The incidence of major complications (greater or equal to grade 3) in those alive after 3 years was 7.7% and 9.3% after 5 years.

  **(Eifel PJ, IJROBP; 1995)**

# GASTROINTESTINAL TOXICITY

- In a more recent randomised Canadian study, 9% of the 126 patients experienced late gastrointestinal toxicity.

  (Pearcey R, JCO; 2002)

- In an analysis of 1784 stage IB patient records treated with RT, small bowel obstruction was observed in 3.9%, 4.3% and 5.3% at respectively 5, 10 and 20 years. Patients who underwent a laparotomy earlier had a higher risk of developing small bowel obstruction.

  (Eifel PJ, IJROBP; 1995)

# GASTROINTESTINAL TOXICITY…

- In a retrospective study in 442 patients receiving radiotherapy by two opposing fields the most frequent late toxicity was in the rectosigmoid. The 5-year actuarial estimate of this late toxicity was 8% (SEE 2%), usually observed in the first year after treatment.

  (Pedersen D, IJROBP; 1994)

- Eifel et al. reported that the risk of developing a severe rectal complication such as severe bleeding, rectal stricture and rectovaginal fistula was 1% per year for the first 2 years after treatment; thereafter the risk was 0.06% per year until 25 years after treatment.

  (Eifel et al,IJROBP; 1995)

# UROLOGICAL TOXICITY

- Marks et al. concluded in their review on urinary bladder, urethra and ureter response to radiation, that acute and late bladder syndromes are two different syndromes.
- The late bladder toxicity appears to be the result of damage to the vascular endothelial cells. (Rubin P, IJROBP;1988)

- The risk of developing severe urinary tract complications such as haematuria, ureteral stenosis and vesicovaginal fistula is stated as 0.7% per year for the first 3 years and thereafter 0.25% per year for at least 25 years.
- There is an actuarial risk at 20 years of 6.2% for grade 3 to 4 urinary toxicity.

(Eifel, IJROBP, 1995)

# TOXICITY TO THE FEMALE REPRODUCTIVE TRACT

- Rectovaginal or vesicovaginal fistulas occurring in **1% to 2%** of the patients treated, are one of the serious complications that can happen to the female reproductive tract.

- Patients treated with radiotherapy experienced deterioration in sexual interest in 49%, frequency of intercourse in 47%, arousal in 42%, lubrication in 46%, orgasm in 49%, pain in 36%, and enjoyment in 47%.

  **(Cull A, Br J Cancer 1993)**

- Eifel et al. described mild spotting in 9.9%, grade 2 toxicity such as dyspareunia, shortening of the vagina length by <5 cm or necrosis after >3 months in **11%** and grade 3 toxicity (severe bleeding) in **12%** of the patients. Vaginal shortening correlated with age at treatment (1% <40years, 2.8% between 40 and 49 years and 6% >50 years).

  **(Eifel et al, IJROBP;1995)**

Randomized studies evaluating radiotherapy with or without chemotherapy do not regularly report late effects on the female genital tract.

# BONE FRACTURES

- Of the 183 cervical cancer patients treated with radiotherapy between 1991 and 1994 at the Royal Marsden Hospital in London, five had severe radionecrosis of the pelvis (2.7%).

  (Blomlie V, Am J Roentgenol 1996)

- Bone mineral densities of the lumbar spine were measured in 40 cervical cancer patients treated with RT and in 40 matched controls. After 1 to 7 years there was no difference in bone mineral densities between the two groups.

  (Chen HH, Radiother Oncol 2002)

# Vascular toxicity

- The assumed pathogenesis of radiation-induced vascular disease is an acceleration of the normal, age-related atherosclerotic process.

  (Butler MJ, Br J Surg 1980)

- In a retrospective study in radiotherapy treated cervical cancer patients between 1960 and 1989, the incidence of long-term vascular toxicity was 0.5%; the actuarial risk at 5, 10 and 20-years was, respectively, 0.1%, 0.5% and 0.8%.

  (Eifel et al, IJROBP;1995)

# SECONDARY MALIGNANCIES

- In 8000 patients a 5.4-fold higher risk to develop uterine sarcoma compared to a control population was observed.

(Czesnin K, Gynecol Oncol 1978)

- 17% of the uterine malignancies in irradiated patients were mixed mesodermal sarcomas; in non-irradiated women, only 5% of uterine malignancies were sarcomas.

(Meredith RF, Cancer 1986)

# RESULTS OF LATE TOXICITY

**TABLE 3** Moderate and severe late toxicity of single modality radiotherapy

| Reference | (23) | (19) | (61) | (58) | (43) | (38) | (64) | (63) | (48) |
|---|---|---|---|---|---|---|---|---|---|
| Patients (*n*) | 123 | 47 | 145 | 398 | 1456 | 1784 | 183 | 116 | 565 |
| *Toxicity* | | | | | | | | | |
| Bowel (all) (%) | 9 | a | a | a | a | a | a | a | a |
| Small bowel (%) | a | 4 | 10 | 5 | 3 | 4 | a | a | a |
| Obstruction (%) | a | a | a | a | 3 | 4 | a | a | a |
| Malabsorption (%) | a | a | a | a | <1 | a | a | a | a |
| Perforation (%) | a | a | a | a | <1 | a | a | a | a |
| Large bowel or rectum (%) | a | 10 | 10 | 7 | 3 | a | 8 | 1 | 6 |
| Proctitis (%) | a | a | a | a | 3 | a | a | a | 2 |
| Rectal stricture (%) | a | a | a | a | 1 | 1 | a | a | a |
| Rectal ulcers (%) | a | a | a | a | <1 | a | a | a | a |
| Rectovaginal fistula (%) | a | a | a | a | 2 | 1 | a | a | a |
| Genitourinary (%) | 7 | 2 | 9 | 6 | 2 | 4 | a | 9 | a |
| Hematuria (%) | a | a | a | a | a | a | a | a | 1 |
| Chronic cystitis (%) | a | a | a | a | 2 | a | a | a | 1 |
| Vesicovaginal fistula (%) | a | a | a | a | <1 | 1 | a | a | 1 |
| Uterovaginal fistula (%) | a | a | a | a | <1 | a | a | a | a |

# RESULTS OF LATE TOXICITY

Summarizes the scarce available data on long-term toxicity for the combined radiotherapy and chemotherapy treatment

**TABLE 5** Moderate and severe late toxicity of combined modality treatment

| Radiotherapy | Split course hyperfractionated | ST | Twice daily | ST | ST | ST | ST |
|---|---|---|---|---|---|---|---|
| Chemotherapy | Cis + 5-FU | Cis | Cis + 5-FU | 5-FU Mit-C | +/–Cis | +/–Cis | Cis + 5-FU |
| Reference | (150)[a] | (10)[a] | (153)[a] | (17)[a] | (154)[a] | (23)[b] | (19)[b] |
| Patients (*n*) | 29 | 60 | 30 | 200 | 59 | 127 | 193 |
| Toxicity | | | | | | | |
| Gastrointestinal problems (%) | – | 4 | 10 | 9 | – | 4 | 9 |
| Radiation proctitis (%) | – | – | – | – | 4 | – | – |
| Rectal bleeding (%) | 3 | – | – | – | – | – | – |
| Rectovaginal fistula (%) | – | – | – | – | 2 | – | – |
| Small bowel problems(%) | 3 | | 3 | – | – | – | 3 |
| Enterocutaneous fistula (%) | 3 | – | – | – | – | – | – |
| Genitourinary (%) | – | – | – | – | – | 10 | – |
| Bladder problems (%) | 3 | 0 | 0 | 3 | – | – | – |
| Vesicovaginal fistula (%) | – | – | – | – | 2 | – | – |
| Ureter obstruction (%) | – | – | – | – | – | – | 2 |
| Renal (%) | – | – | 0 | – | – | – | – |
| Neurological (%) | – | – | – | – | – | 2 | – |
| Hematological (%) | – | – | 0 | – | – | 0 | – |
| Skin (%) | – | – | 3 | – | – | – | <1 |

# RESULTS OF LATE TOXICITY

Chemoradiation in cervical cancer: comparison of long-term toxicity across trials specified

| Trial | Chronic toxicity | Genitourinary | Gastrointestinal | Neurological | Fistula | Other | Overall | Comments | Follow-up | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Minimum | Maximum | Median |
| Keys [17] | Yes | – | – | – | – | – | No diff | Same number of fistula and bowel | 11* | 61* | 36 |
| Morris [23] | Yes | Bladder/ureters | Small/large bowel and rectum | – | – | 34 | No diff | – | 0* | 86 | 43[a] |
| Peters [28] | Yes | 1234 | 1234 | – | – | – | – | – | 12[a] | 72[a] | 42 |
| Pras | No | – | – | – | – | – | – | – | – | – | – |
| Rose [32] | No | – | – | – | – | – | – | – | 5[a] | 65[a] | 35 |
| Tseng [39] | Yes | Radical cystitis | Radical proctitis | 3 + 4 | 3 + 4 | Intestinal obstruction | 3 + 4 | CRT 23.3% RT 12.9% | 12 | 69 | 46.8 |
| Whitney [42] | Yes | – | – | – | – | – | No diff | CRT 16.2% RT 16.5% | 2[b] | 66[b] | – |
| Pearcey [27] | No | – | – | – | – | – | – | CRT6% RT 12% | 6.6 | 102.8 | 65 |
| Hongwei [15] | Yes | 3 | 2 + 3 | – | – | – | No diff | – | – | – | – |
| Wong 89 [44] | No | – | – | – | – | – | – | – | 42 | 72 | – |
| Lira Puerto [20] | No | – | – | – | – | – | – | – | – | – | – |
| Fernandez [10] | No | – | – | – | – | – | – | – | 17 | 48 | 25 |
| Hernandez [14] | No | – | – | – | – | – | – | – | 2 | 49 | 27 |
| Lorvidhaya [21] | No | – | – | – | – | – | – | – | 15 | 59 | 25 |
| Roberts [31] | No | – | – | – | – | – | – | – | - | – | – |
| Singh [35] | No | – | – | – | – | – | – | – | 12? | ? | ? |
| Thomas [37] | Yes | – | – | – | – | – | No diff | – | ? | ? | 59 |
| Wong 99 [45] | Yes | – | – | 2 | 1234 | – | No diff | – | 12 | 130 | 66/96 |
| Leborgne | Yes | – | – | – | – | – | No diff | – | 3 | 51 | 27 |

- It is not yet possible to make firm conclusions on the additive effect of chemotherapy on late toxicities of radiotherapy.
- Based on the current available data the late gastrointestinal and urologic toxicity seem to be comparable in patients treated with or without concomitant Chemotherapy.

# MANAGEMENT OF TOXICITY

Deptt. Of Radiotherapy Oncology PGIMER

# GASTROINTESTINAL TOXICITY

- Late gastrointestinal toxicity is especially attributed to vascular insufficiency (chronic ischaemia) and fibrosis.
- Microscopically, damage to submucosa causing firosis and collagen deposition.
- Late radiation injury to the bowel: malabsorption, small bowel obstruction, chronic proctitis and fistula formation.
- Although gastrointestinal toxicity can occur up to many years after radiotherapy, most patients will develop symptoms during the first 2 years after treatment.

# SMALL BOWEL

- **SMALL BOWEL**, malabsorption and obstruction are the most common complications.
- It occurs usually within the first 2 years after radiation, and affects 2% to 3% of patients.

## DIARRHOEA

- Loperamide or
- Diphenoxylate with atropine.
- Cholestyramine (if excess of Bile Salts in small bowel)
- Low residual diet and stool softeners.

# LARGE BOWEL

## RADIATION PROCTITIS

- Dietary modifications,
- Anti-inflammatory agents,
- Sucralfate/Steroid Enema,
- Formalin therapy (1-4%),
- Thermal or Laser coagulation, and
- Surgical diversion.

Up to now there is no evidence that any one of these treatment options is superior. In the area of therapeutic intervention there is a lack of randomised data on the value of interventions.

# REDUCTION OG GIT COMPLICATIONS

- The use of 3D-conformal radiotherapy/IMRT.
- Use of a belly board device to reduce the irradiated volume of the bowel.
- Treating the patients with full bladder.
- Oral contrast to the patients for better visualizations of the small bowel.
- Surgical displacement of the bowel.
- To do packing ↓GA during Intracavitary brachytherapy to reduce rectal complications.

# UROLOGICAL TOXICITY

- Acute and late bladder toxicites are two different syndromes.
- The late bladder toxicity appears to be the result of damage to the vascular endothelial cells.

## DYSURIA

- Phenazopyridine hydrochloride.

## MILD URINARY FREQUENCY

- Antispasmodics such as oxybutynin, propantheline or imipramine.

# UROLOGICAL TOXICITY....

## SEVERE REDUCTION IN BLADDER CAPACITY

- Bladder augmentation.

## URETHRAL STRICTURES

- Intermittent catheterisation/endoscopic incision or open surgical repair.

## HEMATURIA

- Cystoscopy and selective cauterisation
- Irrigation with various agents such as alum, silver nitrate or dilute formalin (1%)
- Vasopressin infusion
- Hypogastric artery ligation/Cystectomy/bladder diversion if complaints persist.

# Urological toxicity....

## Vesico-vaginal fistulae

- Surgical approaches with debridement and interposition of omentum, muscle, fat and peritoneum.

## Severe cystitis not responding

- candidates for continent urinary reservoirs.

In the absence of controlled trials it is currently not possible to draw firm conclusions regarding the success rate of the several interventions for late radiation cystitis.

# REDUCTION OF URINARY COMLICATIONS

- Use of 3D-CRT/IMRT radiation techniques.
- Treat with four field box technique.
- Packing ↓GA during Intracavitary brachytherapy.
- Use of higher energy beams for patients with higher separations.

# FEMALE REPRODUCTIVE TRACT

- Grigsby et al, have made some suggestions for the treatment of complications of the female reproductive tract.

(Grigsby PW,IJROBP,1995)

## VAGINAL FISTULAE

- Antibiotics and periodic debridement of necrotic tissue.
- Diversion of the urinary or faecal stream and delayed re-anastomosis.

## OVARIAN DYSFUNCTION

- Hormonal replacement should be advocated in pre-menopausal patients.

# FEMALE REPRODUCTIVE TRACT…

## GENERAL RECOMMENDATIONS

- personal hygiene,
- use of topical and systemic hormones,
- vaginal lubrication,
- Vaginal dilator or vaseline tampon.
- case of sexual problems counselling should be recommended to the patient and partner.

# BONE FRACTURES

- Although never prospectively investigated, recommended drug treatments are:
  - progestins,
  - conjugated estrogens,
  - calcium supplements and bisphosphonates.

- For symptom relief some authors recommended non-steroidal anti-inflammatory drugs.

(Moreno A, Int J Radiat Oncol Biol Phys 1999)

# CONCLUSION

- In view of the consistency and extent of the survival benefit for chemoradiation the additional acute toxicity described is justified.
- However, the issue of late toxicity still needs to be resolved since there is a lack of reliable data.
- The absence of a uniform classification system for reporting treatment morbidity has resulted in a considerable inconsistency in the reporting of treatment complications in cervical cancer patients.

# CONCLUSION

- Presently, most of the authors are using the NCI CTCAE Ver 3.0 for reporting the acute toxicity and RTOG/EORTC scoring system for the late toxicity although there is no general consensus for the same.
- For the future it will be of major importance to register acute and late treatment side effects consistently.
- We therefore think that these and future randomized trials should systematically collect chronic toxicity data using a standard data collection forms.
- Randomized trials should report the actuarial rates of the toxicity.