FACULTY OF MEDICINE AND HEALTH SCIENCES

RADIOTHERAPIE-ONCOLOGIE
VAKGROEP STRUCTUUR EN HERSTEL VAN DE MENS

NEVENWERKINGEN BIJ ABDOMINALE EN PELVIENE RADIOTHERAPIE

K. Vandecasteele, Radiotherapeut-Oncoloog

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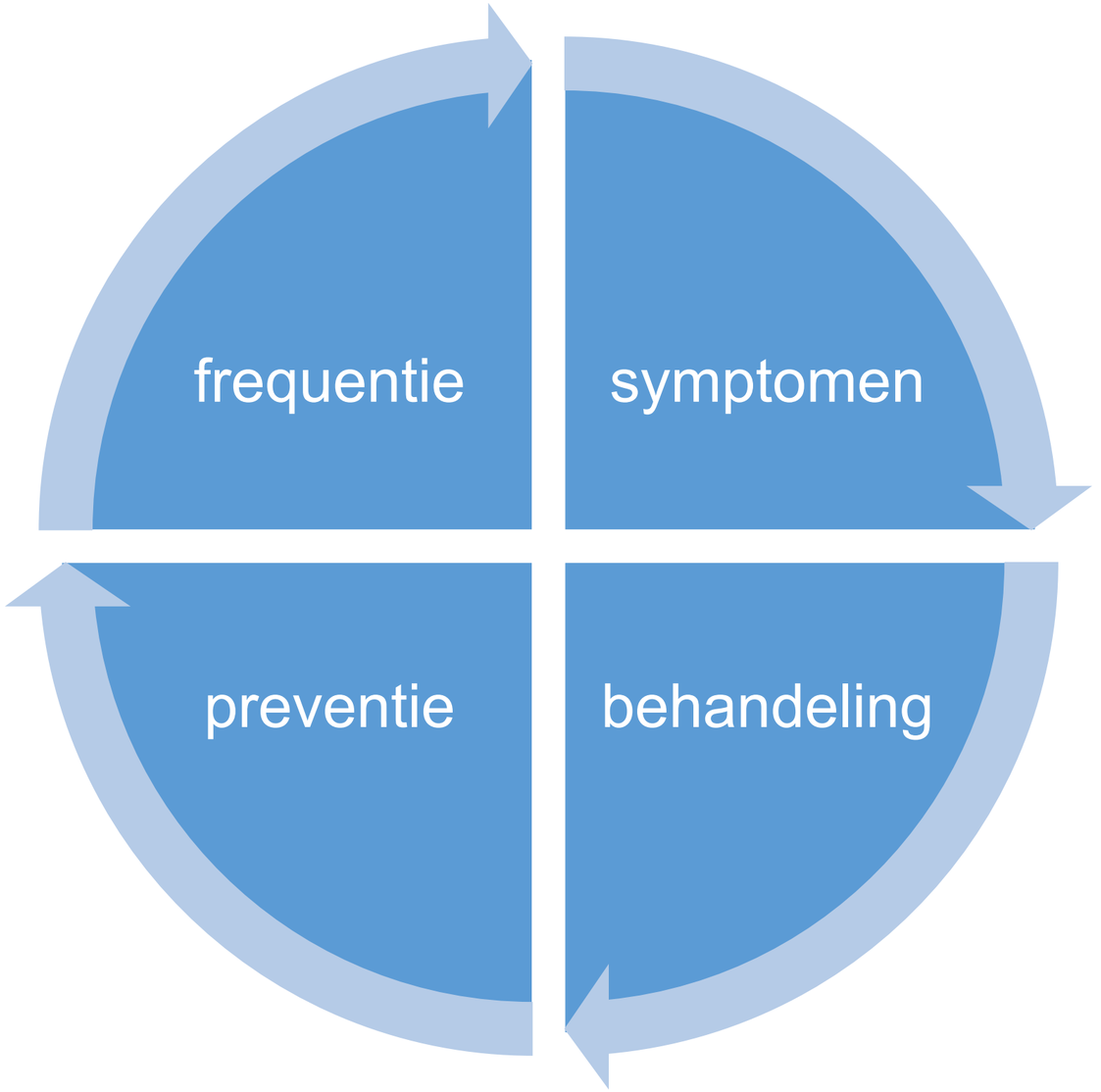
TOPICS DEZE AVOND

- Gastro-intestinaal
- Urinair
- Genito-sexueel
- Huid
- Bot/beenmerg
- Lymphoedeem



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GASTRO-INTESTINALE TOXICITEIT

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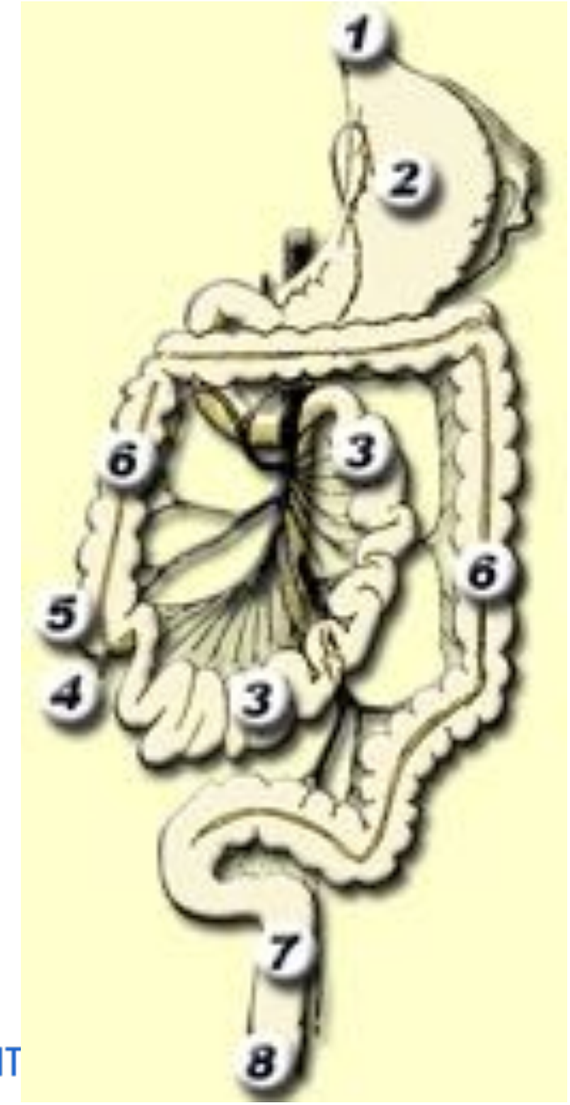
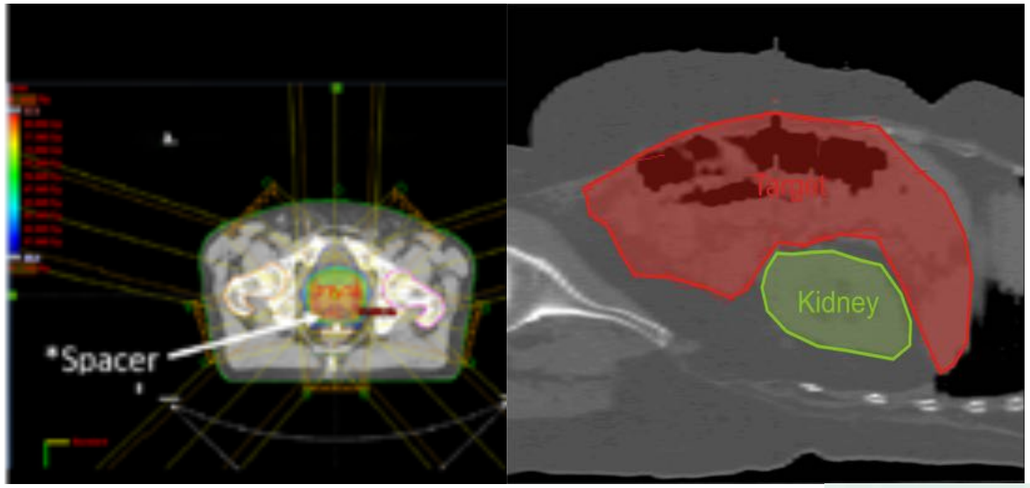
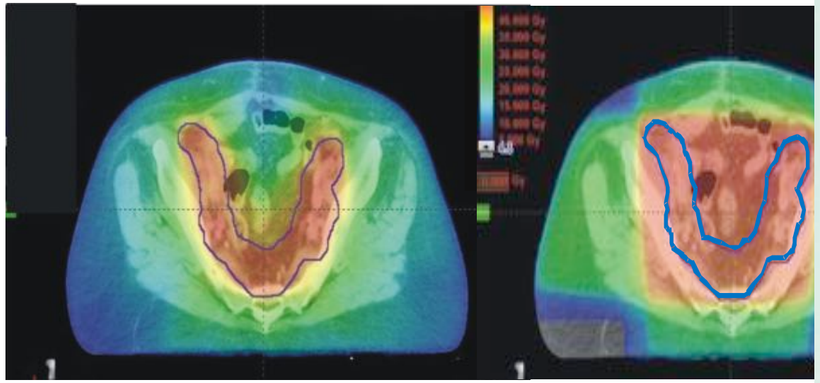
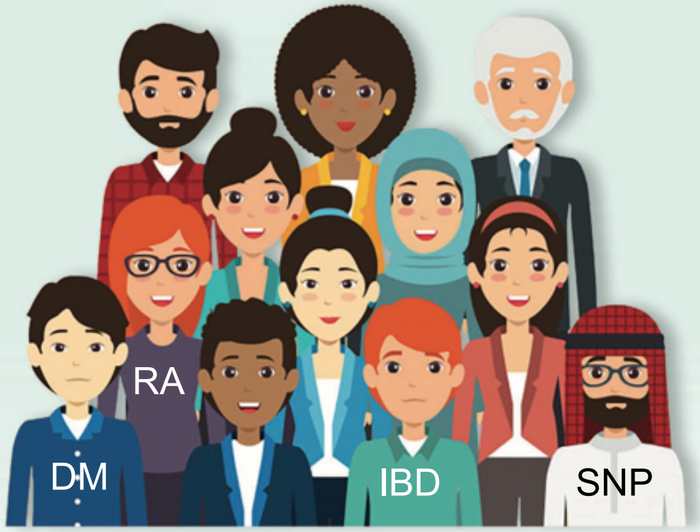
TOXICITEIT BEPALENDE FACTOREN









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TOXICITEIT RT PROSTAATCA (prostaat + pelvis)

ACUUT

UPPER GI

Grade 0	Grade 1	Grade 2	Grade 3
86	12	2	0

LOWER GI

Grade 0	Grade 1	Grade 2	Grade 3
8	39	51	2

Behandeling

Symptomatisch bv. Anti-emetica (Zofran), loperamide, anti-spasmolytica, …

LAAT

UPPER GI

Grade 0	Grade 1	Grade 2	Grade 3
94	6	0	0

LOWER GI

Grade 0	Grade 1	Grade 2	Grade 3
27	57	12	4

Behandeling

vaak enkel symptomatisch. Oorzaak?

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SYMPTOMEN

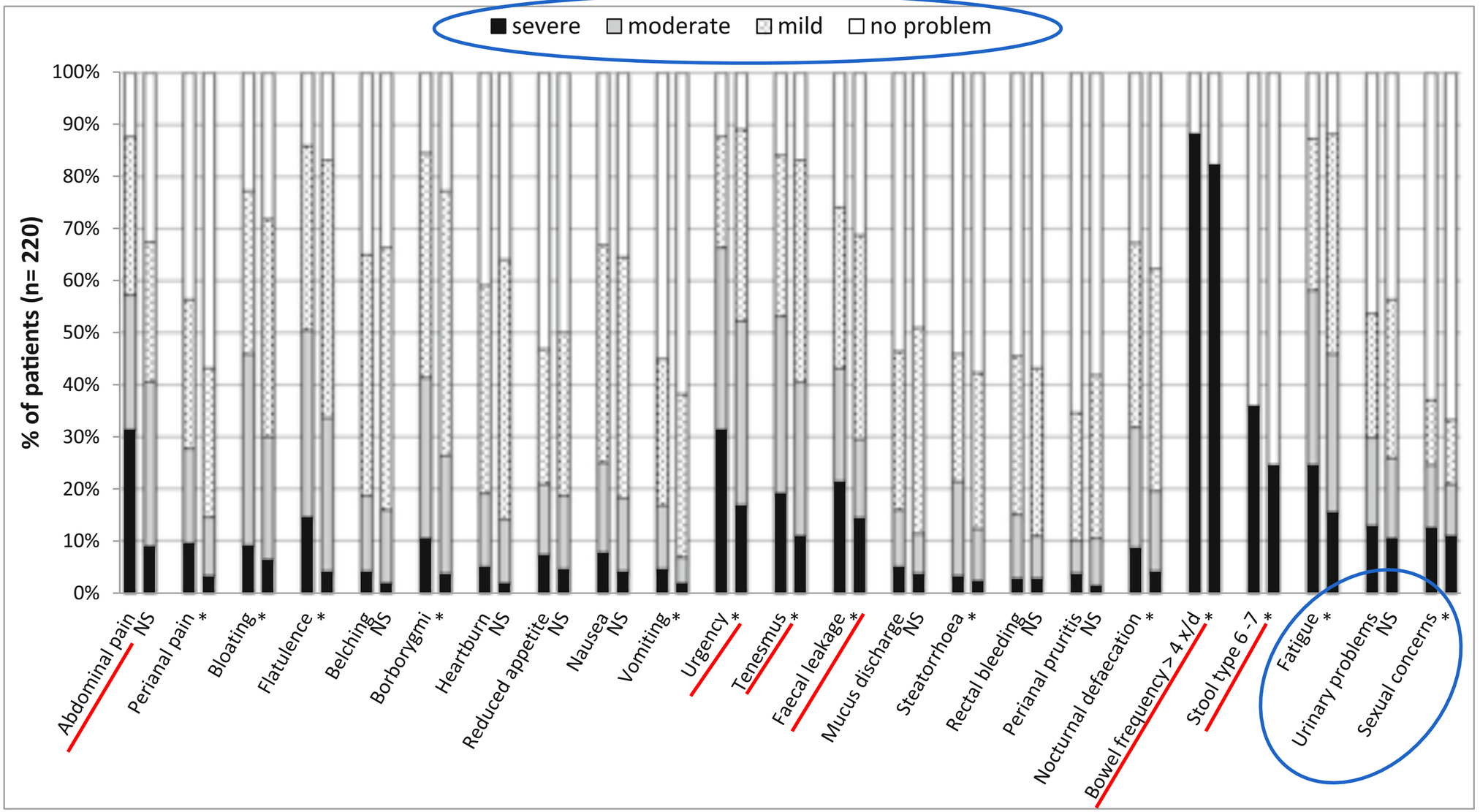

Fig. 1 Paired symptom scores ($n = 220$) at baseline and discharge; left bar, baseline assessment; right bar, discharge assessment (NS, not significant, $^*p < 0.05$)

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OORZAKEN

1 op 2 !

1 op 3 !

Table 2 Prevalence of new gastrointestinal or nutritional diagnoses ($n = 220$)

Diagnosis	Prevalence, *n* (%)
Vitamin D deficiency	133 (60%)
Small intestinal bacterial overgrowth	118 (54%)
Bile acid malabsorption	104 (47%)
Gastritis	68 (31%)
Vitamin B_{12} deficiency	65 (30%)
Weak pelvic floor musculature on rectal exam	36 (21%)
Telangiectasia on the rectal wall	33 (15%)
Trace element deficiency	31 (14%)
New GI polyp	24 (11%)
Hiatus hernia	22 (10%)
Faecal loading (confirmed on abdominal X-ray)	18 (8%)
Dietary fibre excess on fibre quiz	16 (7%)
Oesophagitis	16 (7%)
Iron deficiency	16 (7%)
Pancreatic insufficiency	16 (7%)
Duodenitis	13 (6%)
Thyroid problems	11 (5%)
Diverticular disease	9 (4%)
Gastro-oesophageal reflux disease	8 (4%)
Haemorrhoids	7 (3%)
Inflammatory bowel disease	4 (2%)
Rectal ulcer	4 (2%)
New GI cancer	5 (2%)
Anal fissure/anal sphincter defect	3 (1%)

Vit D deficiëntie:

- suppletie!
- Essentieel voor Ca2+ absorptie in populatie at risk voor botfractuur.

Vit B12 deficiëntie:

- suppletie!
- vermoeidheid
- gelinkt aan geheugenproblemen, anemie en kortademigheid
- Vaak veroorzaakt door bacteriële overgroei (nr 2!) en/of galzuur malabsorbtie

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Muls et al. Support Care Cancer 2020

Andreyev et al. Lancet 2013

OORZAKEN

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Bacteriële overgroei in de dundarm

- Diagnose en interpretatie zeer moeilijk!
- Ademtest = 1e lijn
- Duodenaal aspiraat kan gidsen in evtl AB-therapie (indien toch gastroscopie voor gastritis?)

Galzuurdiarree

- 1% (nl populatie) vs 47%
- Malabsorptie van galzuren in terminale ileum door (chemo)radiotherapie
- Waterige stoelgang maar ook urgency zonder incontinentie!
- Kan gemaskeerd worden door opioiden of anti-diarree maatregelen
- SeHCAT-test (galzuurresorptietest)
- Behandeling: cholestyramine, galzuurbindend hars

Muls et al. Support Care Cancer 2020

Andreyev et al. Lancet 2013

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OORZAKEN

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Algoritmes !?!?!?

Elke klacht apart!

Muls et al. Support Care Cancer 2020

Andreyev et al. Lancet 2013

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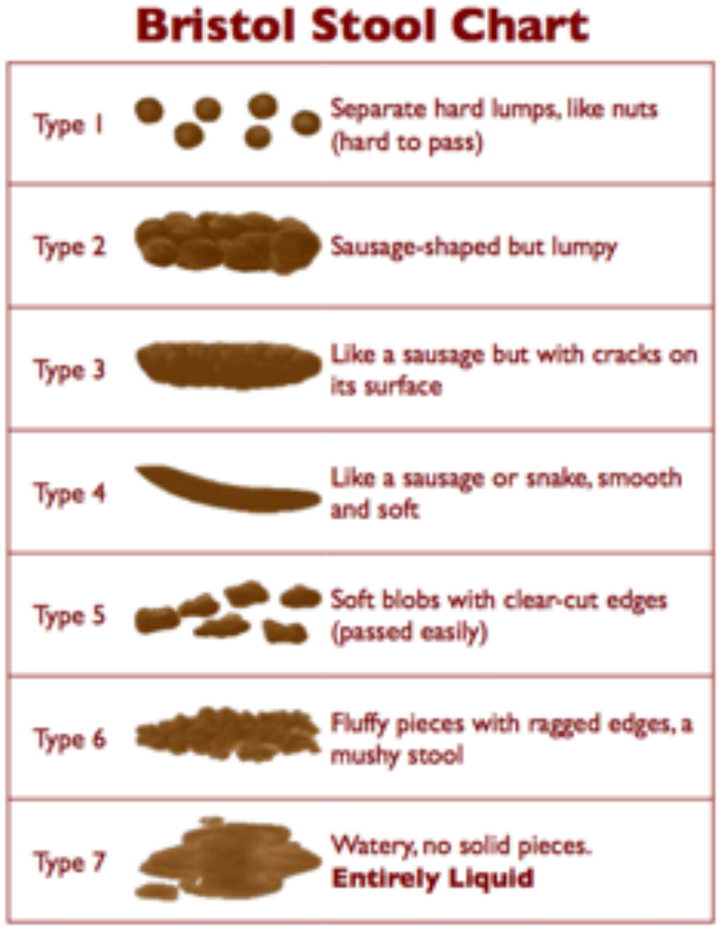
DIARREE OF TYPE 6-7 STOELGANG



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Andreyev et al. Frontline Gastroenterology 2015
KW Heaton, University of Bristol

Diarrhoea (stool type 6–7 Bristol Stool Chart)
Also use this section if patient has 'frequency of defecation', 'nocturnal defecation' or 'urgency of defecation'

Investigations	Potential results	Clinical management plan: abnormal results
Dietary/ lifestyle/ medications assessment	High dietary fat intake Low/high fibre intake High fizzy drink intake High use of sorbitol-containing chewing gum or sweets High caffeine intake High alcohol intake Anxiety Drug induced, eg, PPIs Laxatives β blockers Metformin	1. Dietary advice about healthy fibre and dietary fat intake. 2. Referral to dietitian and ask patient to complete 7-day dietary diary beforehand. 3. Lifestyle advice about smoking cessation. 4. Consider referral for psychological support. 5. Medications advice. 6. Antidiarrhoeal ± bulk laxative.
Routine AND additional blood screen (pages 2–3)	Abnormal results Mg^{2+} low Coeliac disease	Follow treatment of abnormal blood results (pages 2–3). 1. If IgA deficient, request IgG coeliac screen. 2. Confirm with duodenal biopsy. 3. Refer to dietitian for gluten free diet. 4. Liaise with GP regarding long term monitoring of bone densitometry and referral to a coeliac clinic.
Stool sample: for microscopy, culture and *Clostridium difficile* toxin	Stool contains pathogen	Treat as recommended by the microbiologist and local protocols.
Stool sample: for faecal elastase	EPI	See EPI (page 16)
OGD with duodenal aspirate and biopsies and/or glucose hydrogen (methane) breath test	SIBO	Treatment for SIBO (page 17).
Carbohydrate challenge	Specific disaccharide intolerance	Appropriate treatment (pages 16–17).
SeHCAT scan	BAM	Treatment for BAM (page 16).
Abdominal X-ray	Faecal loading with overflow	Bulking agent.
1st Line		
Flexible sigmoidoscopy with biopsies from non-irradiated bowel (avoid biopsies from areas obviously irradiated in sigmoid and rectum)	Radiation proctopathy and frequency of defecation	1. Pelvic floor and toileting exercises (page 18)—min. 6 weeks. 2. Add stool bulking agent to pelvic floor exercise regimen. 3. Antidiarrhoeal ± stool bulking agent.
	Radiation proctopathy/colopathy and pelvic floor dysfunction (page 17)	1. Antidiarrhoeal. 2. ± stool bulking agent. 3. ± pelvic floor and toileting exercises (page 18).
	Macroscopic colitis	1. Send stool culture. 2. If mild or moderate, refer within 2 weeks to a gastroenterologist. If severe, ***this is an emergency***—discuss immediately with a gastroenterologist.
	Microscopic colitis	Discuss with supervising clinician and refer to a gastroenterologist.
2nd Line		
Colonoscopy with biopsies	Macroscopic or microscopic colitis Organic cause (eg, infection, inflammation, neoplastic)	As above. Discuss with the appropriate clinical team within 24 h.
If diarrhoea is present in combination with other symptoms: flushing, abdominal pain, borborygmi, wheezing, tachycardia or fluctuation in BP		
3rd Line		
Gut hormones (Chromogranin A&B, gastrin, substance P, VIP, calcitonin, somatostatin, pancreatic polypeptide) and Urinary 5-HIAA and CT chest, abdomen and pelvis	Functioning NET, eg, carcinoid syndrome or pancreatic NET	Discuss and refer to the appropriate neuroendocrine tumour team requesting an appointment within 2 weeks.
	If all tests are negative, but symptoms persist	Reassure and suggest symptomatic treatment with antidiarrhoeal drugs. Trial of low-dose tricyclic antidepressants. Biofeedback.

Note: faecal calprotectin as a marker for bowel inflammation is too non-specific and hence not recommended in this population.
BAM, bile acid malabsorption; EPI, exocrine pancreatic insufficiency; GP, general practitioner; IgA, immunoglobulin A; IgG, immunoglobulin G; OGD, oesophago-gastroduodenoscopy; PPI, proton pump inhibitor; NET, neuroendocrine tumour; SIBO, small intestinal bacterial overgrowth.

SYMPTOMEN

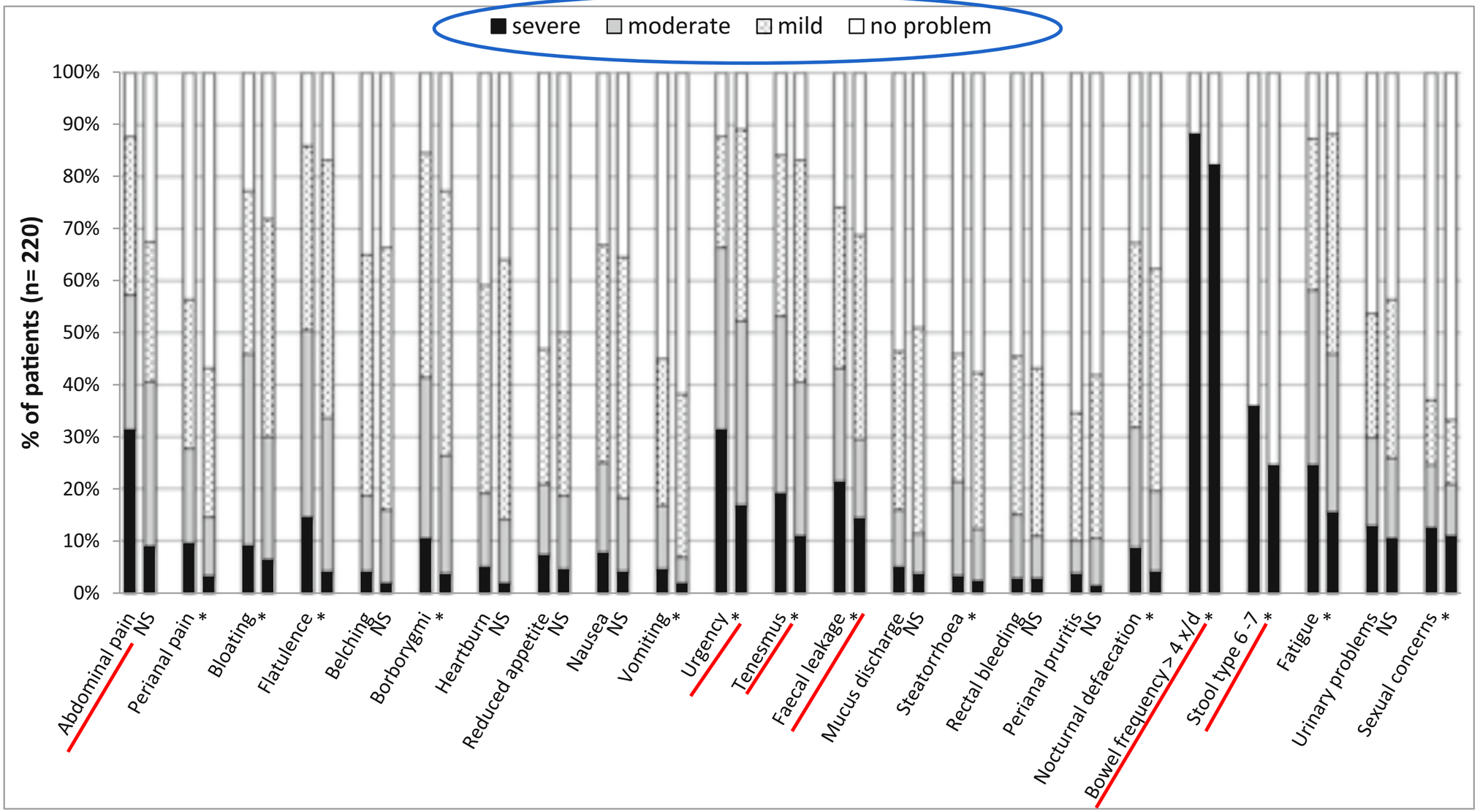

Fig. 1 Paired symptom scores ($n = 220$) at baseline and discharge; left bar, baseline assessment; right bar, discharge assessment (NS, not significant, $*p < 0.05$)

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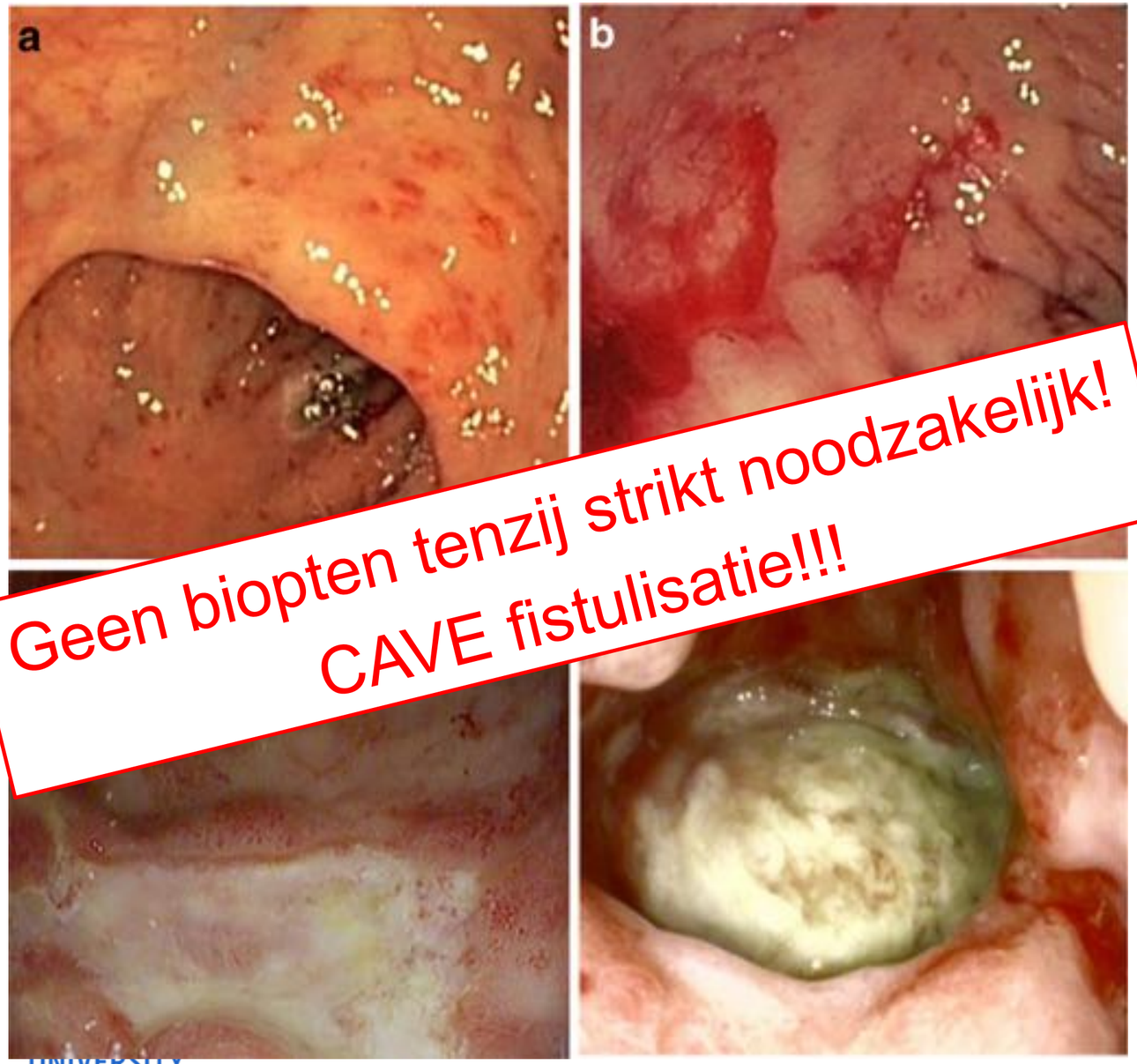
Muls et al. Support Care Cancer 2020

CHRONISCHE RADIATIE PROCTITIS



Geen biopten tenzij strikt noodzakelijk!
CAVE fistulisatie!!!

A: oedemateuse CRP met multipele niet-confluente telangiëctasieën

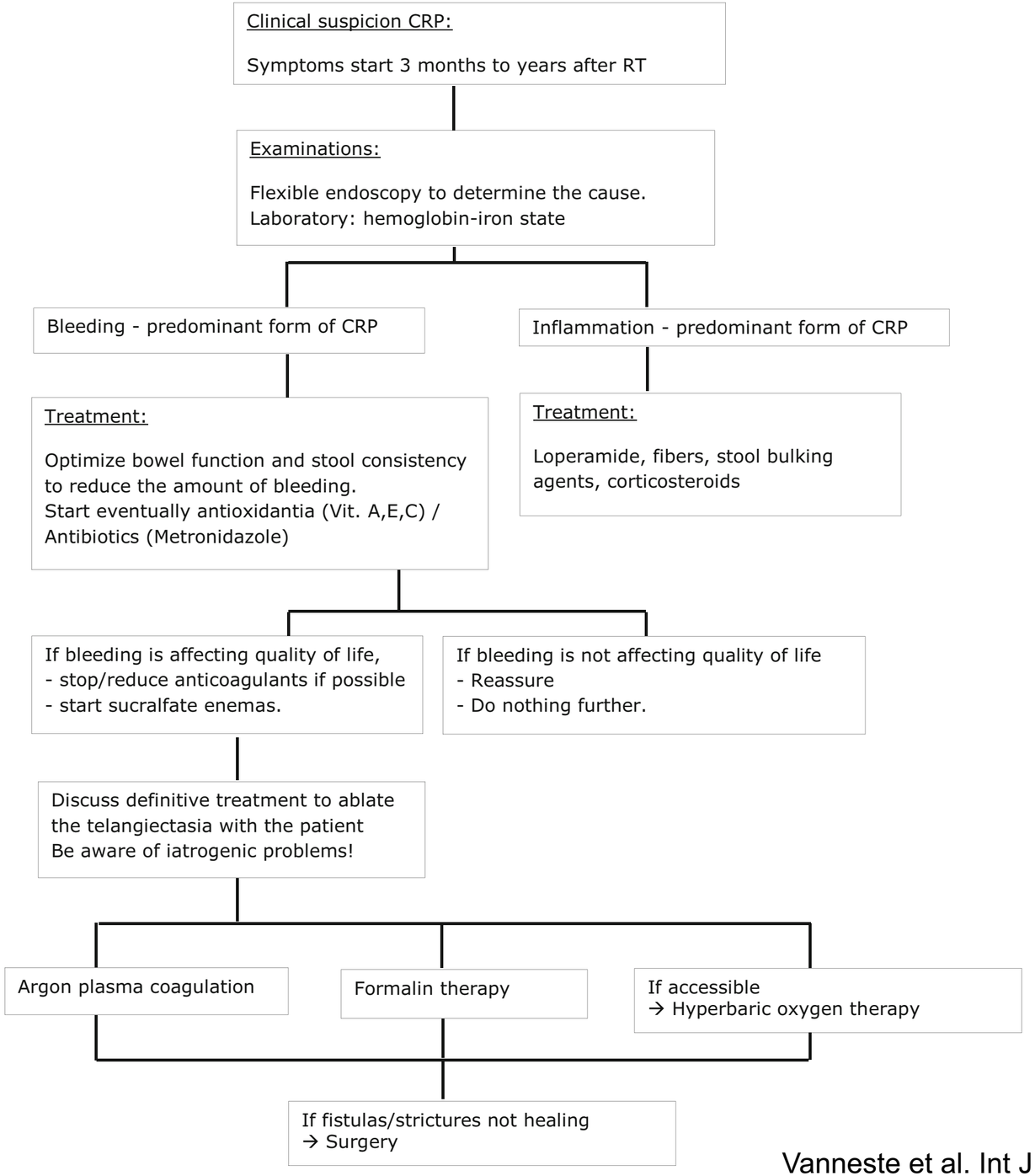
B: predominant bloedend CRP

C: necrose met multipele confluente telangiëctasieën

D: ulcus

Vanneste et al. Int J Colorect Dis 2015: 30:1293 - 1303

BEHANDELING



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Vanneste et al. Int J Colorect Dis 2015: 30

PREVENTIE?

We included 92 RCTs involving more than 10,000 men and women undergoing pelvic radiotherapy.

Cochrane Database of Syste

Authors' conclusions

Conformal radiotherapy techniques are an improvement on older radiotherapy techniques. IMRT may be better than 3DCRT in terms of GI toxicity, but the evidence to support this is uncertain. There is no high-quality evidence to support the use of any other prophylactic intervention evaluated. However, evidence on some potential interventions shows that they probably have no role to play in reducing RT-related GI toxicity. More RCTs are needed for interventions with limited evidence suggesting potential benefits.

dverse
pelvic radiotherapy for primary
(Review)

Lawrie TA, Green JT, Beresford M, Wedlake L, Burden S, Davidson SE, Lal S, Henson CC, Andreyev HJN

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URINAIRE TOXICITEIT

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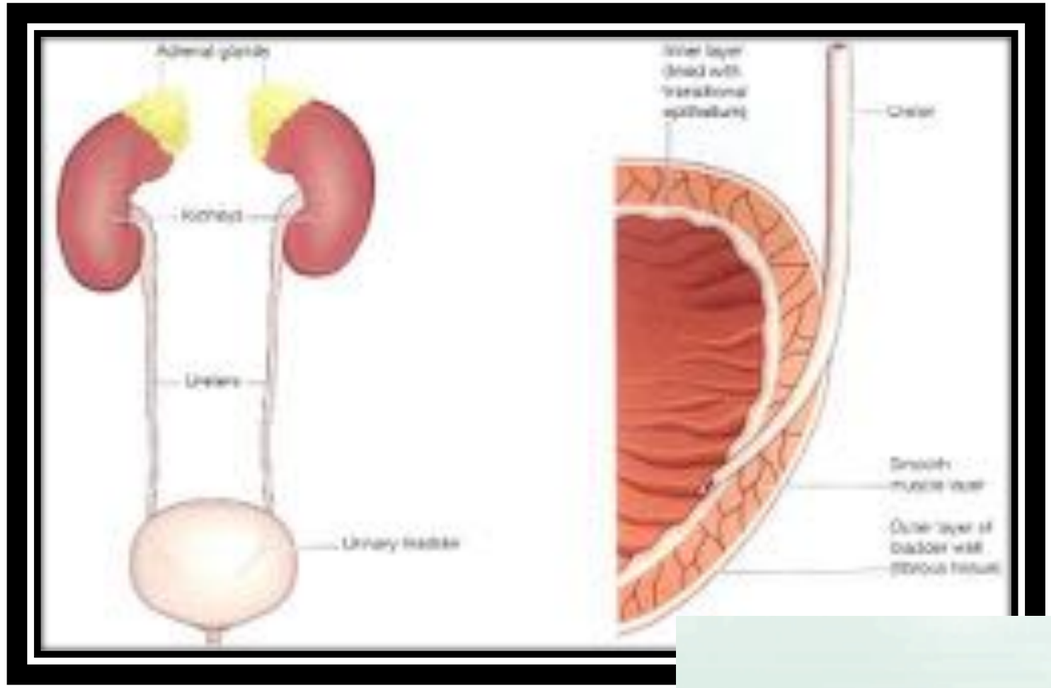
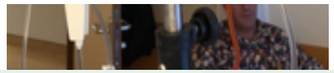
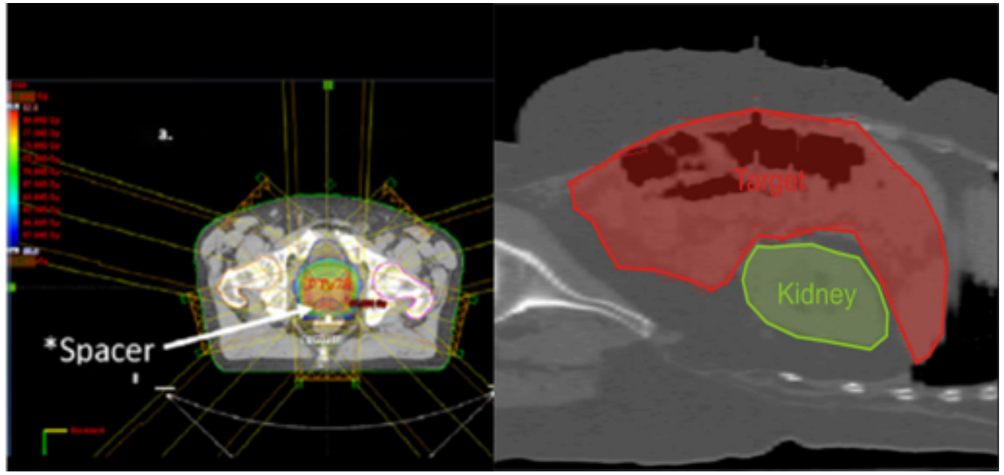
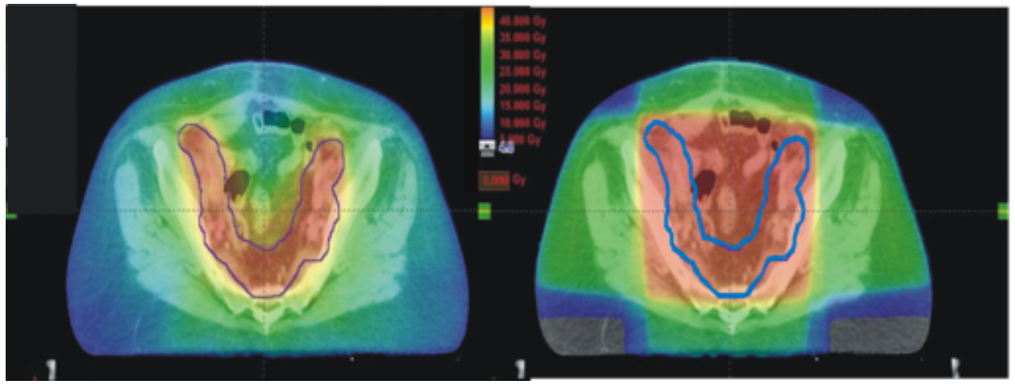
TOXICITEITSBEPALENDE FACTOREN



cyclofosfamide







Bladder wall (outer 3 mm of the bladder solid volume):

V30 <30cm³
V82 <7 cm³

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URINAIRE TOXICITEIT RT PROSTAATCA (UZG)

TIMING	GRAAD	Prostaat (N=278)	Prostaat + pelvis
ACUUT	G1	25%	37%
	G2	37%	43%
	G3	6%	6%
LAAT	G1	19%	53%
	G2	10%	18%
	G3	1%	6%

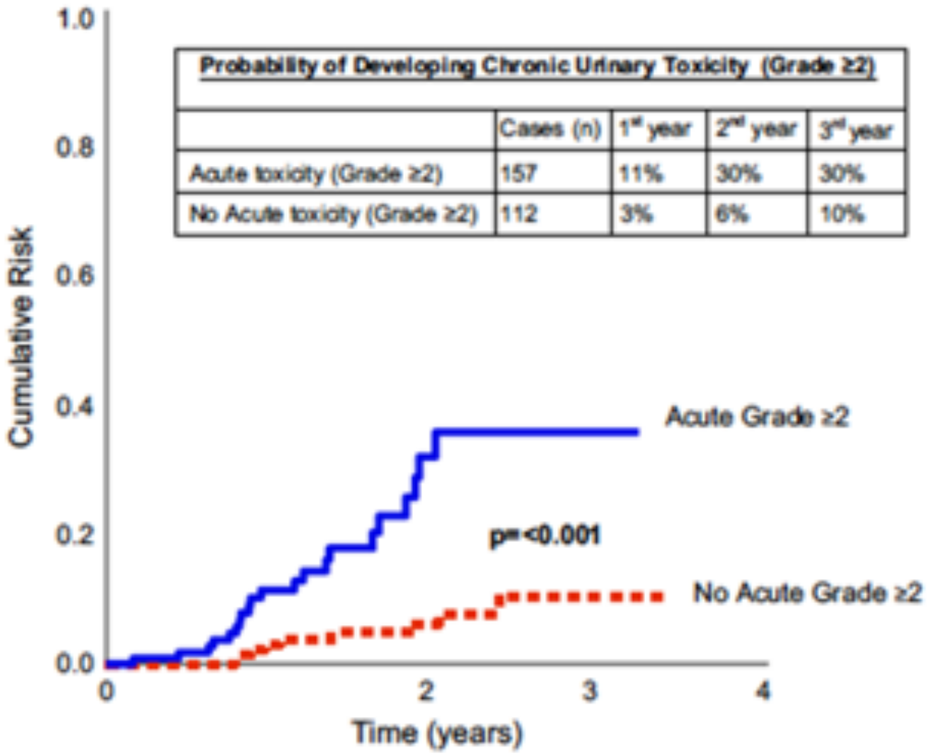

Fig. 2. Cumulative risk of chronic urinary toxicity (Grade ≥2) by the occurrence of acute toxicity (Grade ≥2).

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Harsolia et al. IJROBP 2007, 69 (4)

Prof. Fonteyne en prof. Ost, toxiciteitsdata prostaat

SYMPTOMEN EN BEHANDELING

Symptomen	Behandeling = Symptomatisch
Dysurie	UWI uitsluiten! Phenazopyridine, NSAIDs, (corticoiden)
Nycturie, pollakisurie, blaasspasmen	Anticholinergica (uroloog! glaucoom!)
Obstructief blaaspatroon	Selectieve α1-blokker
Hematurie	Diurese, verwijzing uroloog (flow-chart)
…	…

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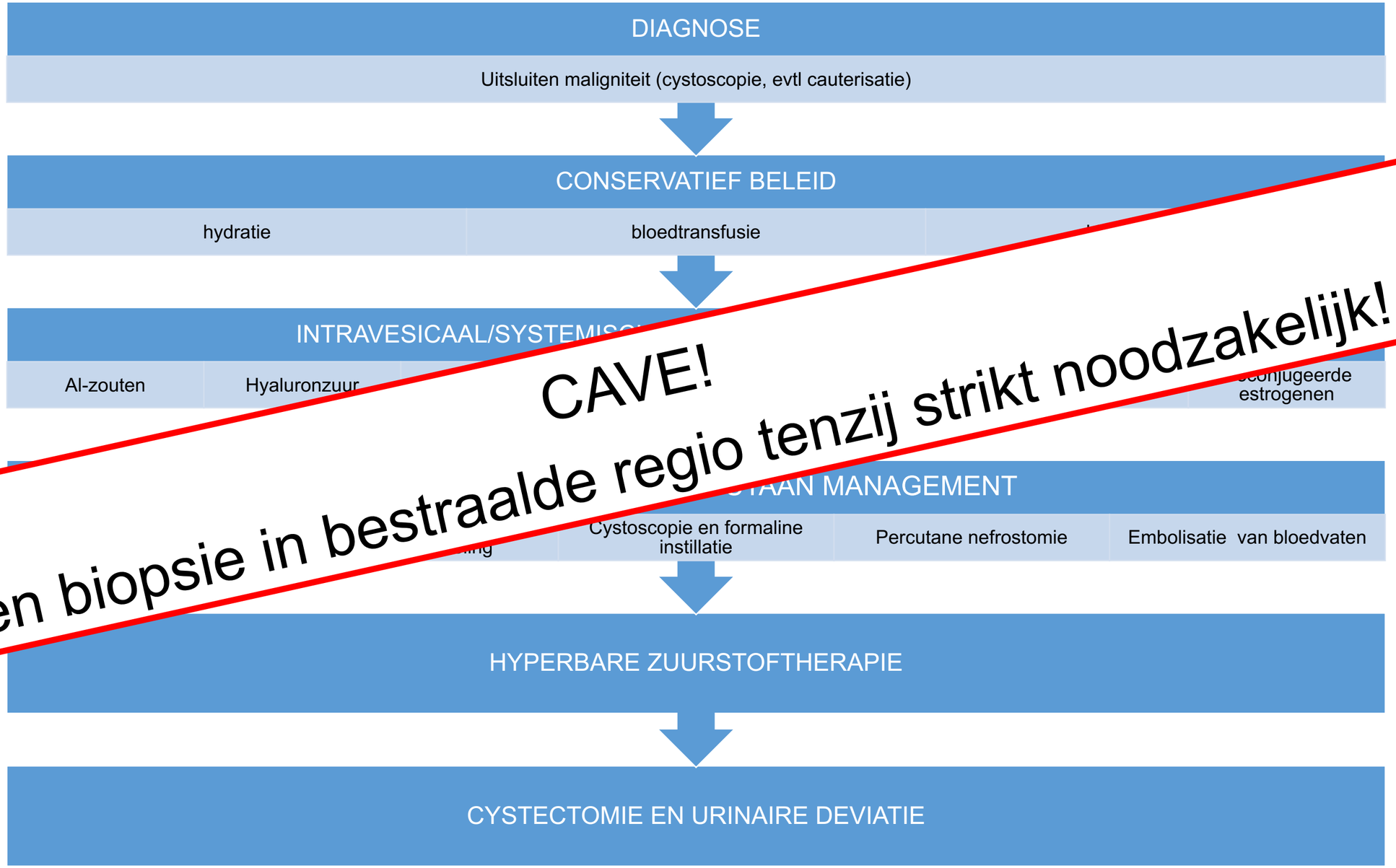
BELEID HEMORRHAGISCHE RADIATIE-CYSTITIS



CAVE!

Geen biopsie in bestraalde regio tenzij strikt noodzakelijk!

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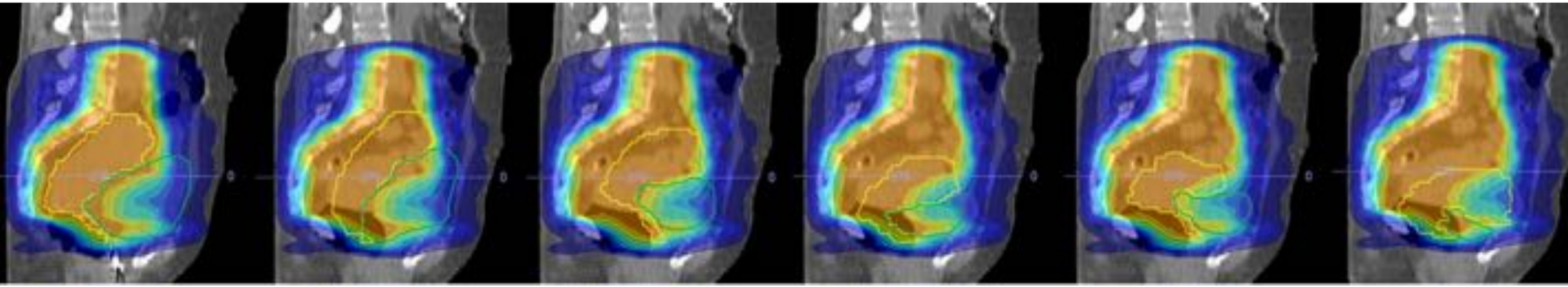
Radiation therapy for pelvic malignancy and its consequences, Springer, 2015

PREVENTIE?

- Niet medicamenteus
- Behandeling met een comfortabel gevulde blaas.



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GENITO-SEXUELE TOXICITEIT (INCL. HUID)

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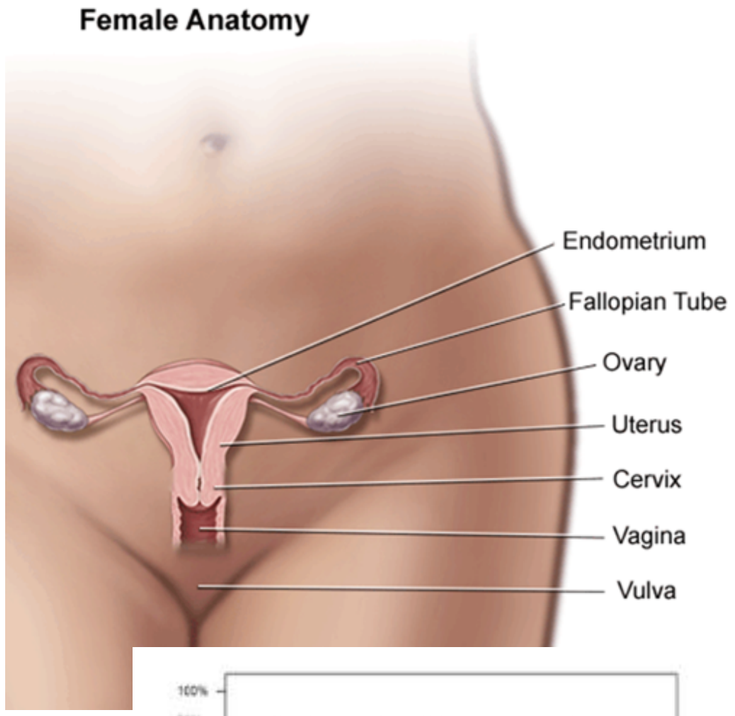
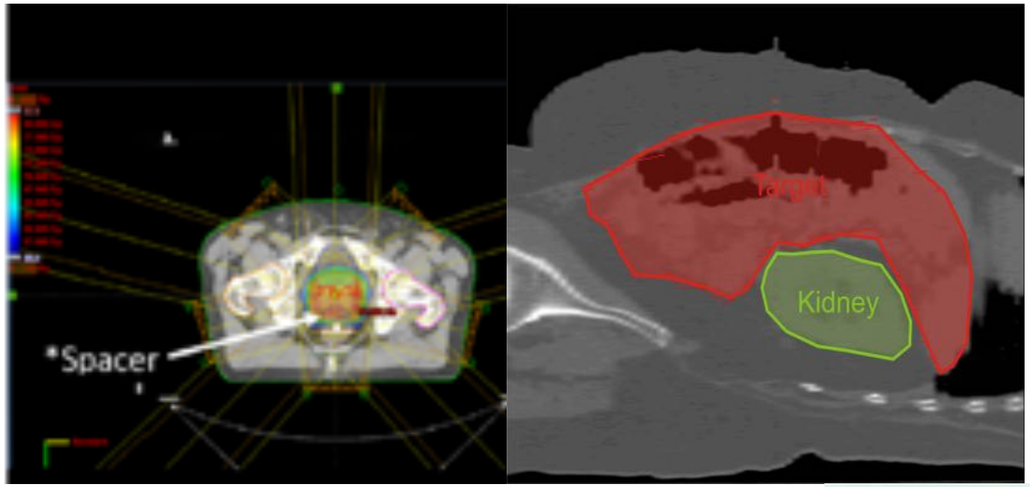
TOXICITEIT BEPALENDE FACTOREN





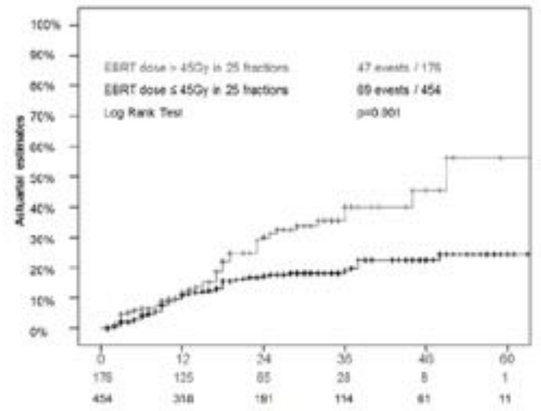
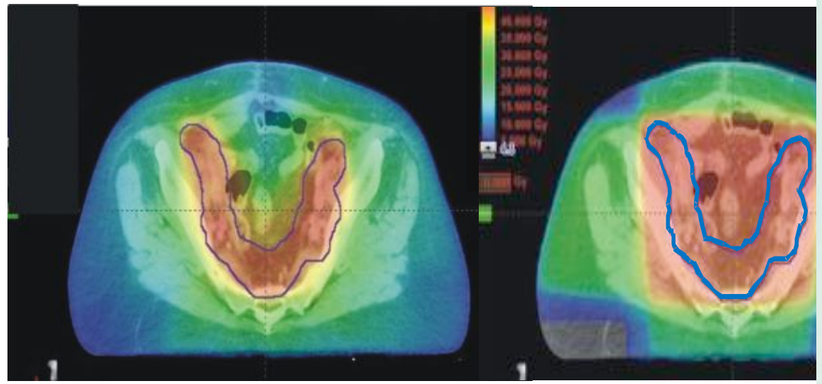
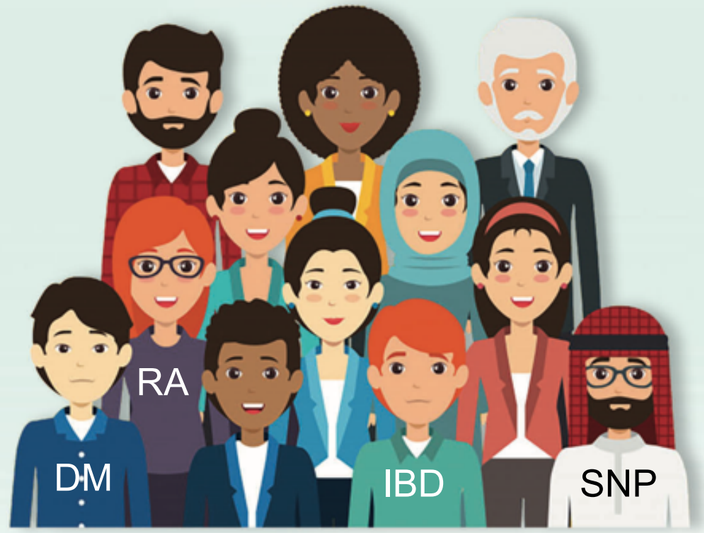


Fig. 3. Actuarial estimates for vaginal stenosis G ≥ 2 in patients according to the EBRT dose.





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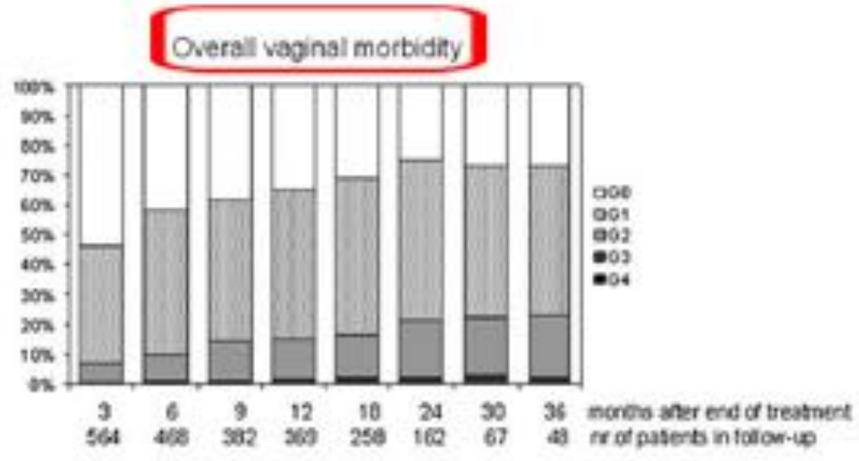
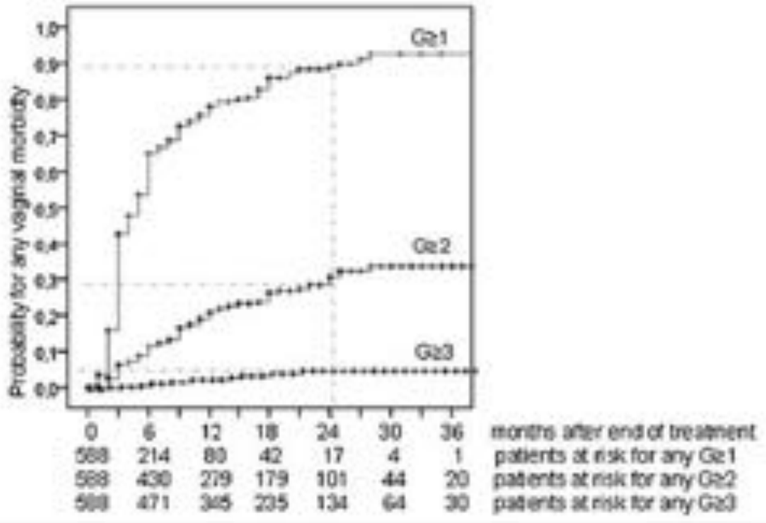
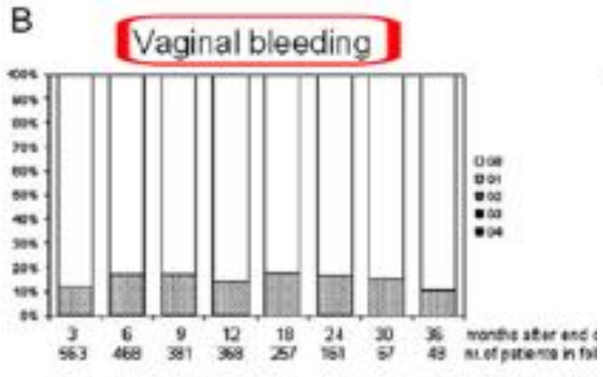
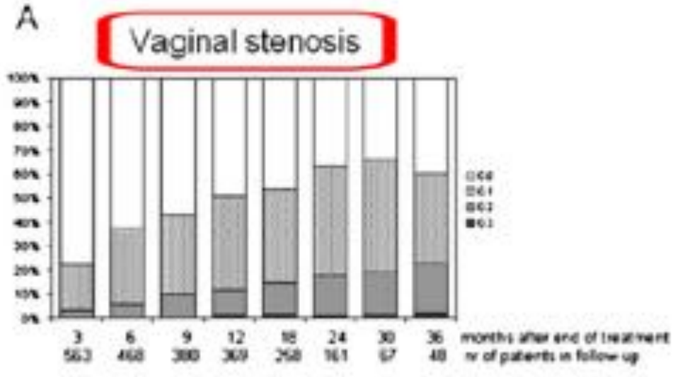
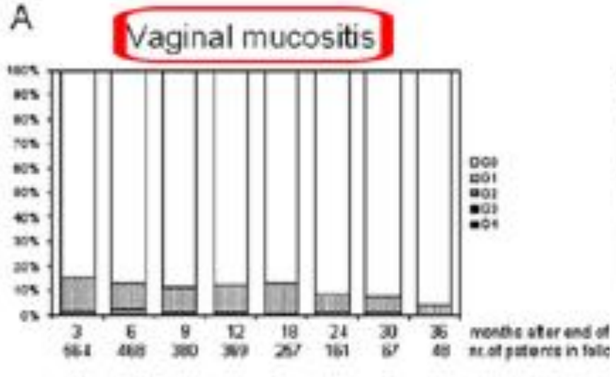
VAGINALE MORBIDITEIT NA CRT/BT CERVIX

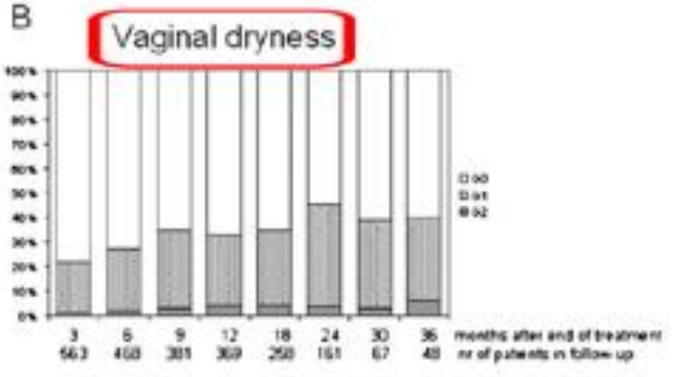












Vaginale toxiciteit
scoring systemen

- Gradatie van de ernst

CTCAE 4.0 of 3.0	vernauwing tot obstructie: G1 - G3
LENTSOMA	klinische last: G1 – G4
RTOG / EORTC	morfologische beschrijving: G 1 – G4

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SEKSUELE MORBIDITEIT = COMPLEX

The Assessment and Management of Sexual Difficulties after Treatment of Cervical and Endometrial Malignancies

I. D. White

Table 1 — Summary of factors contributing to sexual difficulties in women receiving pelvic radiotherapy

Physical factors	Psychological factors	Sexual consequences
Vaginal dryness	Fear of sex causing cancer recurrence	Loss of sexual desire
Vaginal stenosis	Fear of transmitting cancer to partner via sexual contact	Arousal difficulties
Vaginal shortening	Fear of contaminating partner with radioactivity	Delayed orgasm
Vaginal bleeding	Fear of sexual pain	Anorgasmia
Vaginal discharge	Anxiety	Altered orgasmic sensation
Vulvovaginitis	Depression	Superficial dyspareunia
Menopausal symptoms	Fatigue	Deep dyspareunia
Perineal skin reactions	Altered self-concept	Secondary vaginismus
Cystitis	Altered femininity	Reduced sexual satisfaction
Proctitis	Poor couple communication	Sexual aversion
Diarrhoea	Woman and partner coping styles	
Infertility		
Reduced bladder/bowel control		

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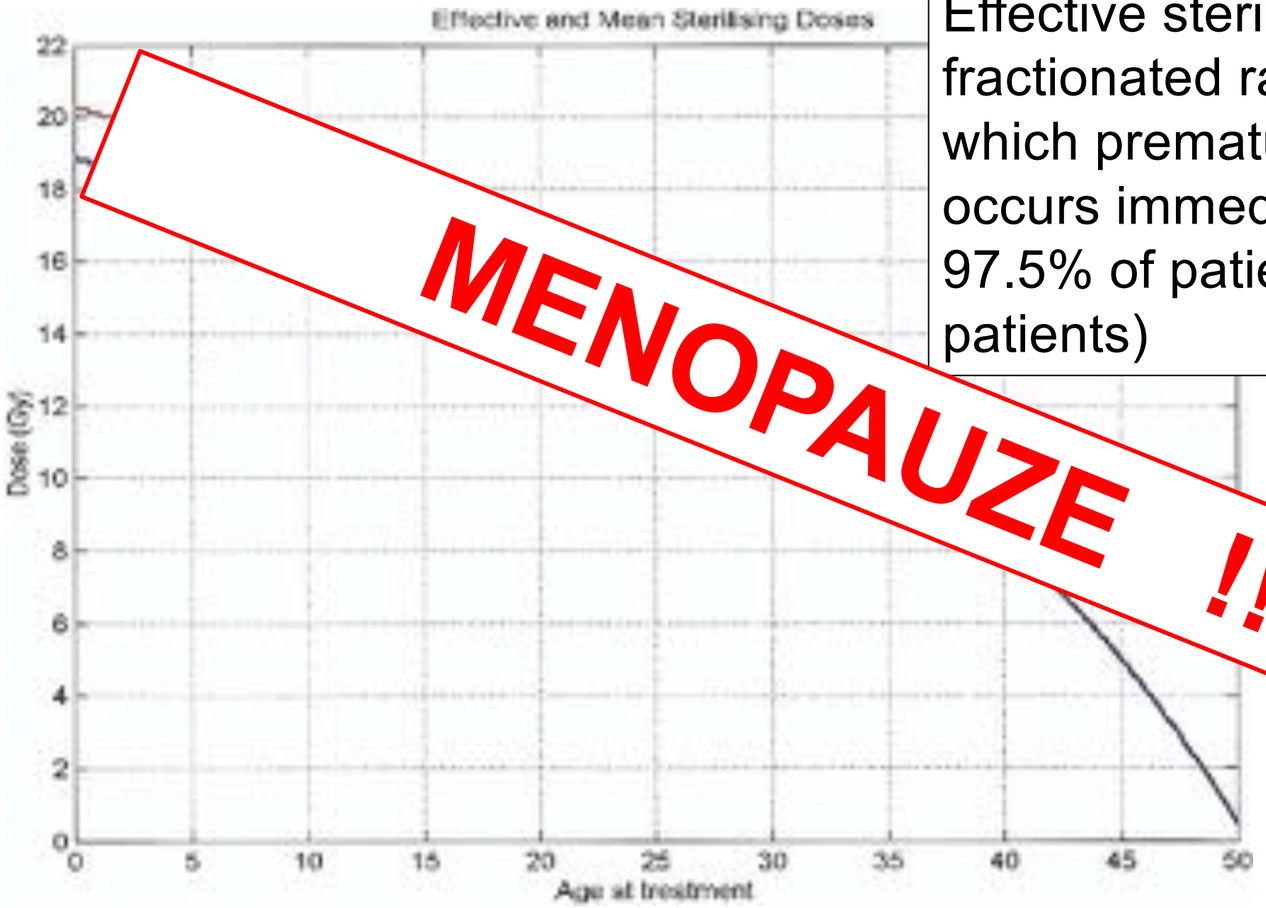
Clinical Oncology, 2008

OVARIA



Effective sterilizing dose = dose of fractionated radiotherapy [Gy] at which premature ovarian failure occurs immediately after treatment in 97.5% of patients. (mean = 50% of patients)

MENOPAUZE !!!

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Fig. 3. The effective (red, upper) and mean (blue, lower) sterilizing dose of radiation for a known age at treatment.

Wallace et al. IJROBP 62(3)

LEVENSKWALITEIT EN SEXUEEL FUNCTIONEREN

TABLE 2. QoL scores between primary surgery and primary radiotherapy (means ± SD)

	RHL (n = 263)	PRT (n = 60)	*P*
EORTC QLQ-C30			
Functioning scales	mean ± SD	mean ± SD	
Physical functioning	88.7 ± 14.8	81.7 ± 20.8	0.003
Role functioning	84.2 ± 23.6	77.8 ± 27.4	0.068
Emotional functioning	77.3 ± 22.1	78.2 ± 23.9	0.792
Cognitive functioning	82.1 ± 22.4	82.5 ± 23.3	0.909
Social functioning	82.4 ± 23.0	71.1 ± 31.6	<0.001
Global Health-QoL	78.7 ± 60.3	70.7 ± 25.1	0.313
Symptom scales			
Fatigue	28.3 ± 25.6	32.4 ± 27.7	0.266
Nausea and vomiting	4.5 ± 12.5	6.4 ± 12.7	0.293
Pain	15.4 ± 24.1	18.3 ± 26.7	0.405
Single-item scales			
Dyspnoea	11.1 ± 19.2	10.0 ± 17.7	0.670
Insomnia	23.8 ± 28.8	31.1 ± 33.0	0.087
Appetite loss	6.7 ± 18.5	11.1 ± 19.1	0.099
Constipation	16.5 ± 26.2	8.9 ± 20.2	0.036
Diarrhoea	7.3 ± 16.1	16.7 ± 26.4	<0.001
Financial difficulties	11.8 ± 25.4	22.2 ± 35.7	0.009

TABLE 2. QoL scores between primary surgery and primary radiotherapy (means ± SD)

	RHL (n = 263)	PRT (n = 60)	*P*
EORTC QLQ-CX24			
Multi-item scales	mean ± SD	mean ± SD	
Symptom experience	13.6 ± 11.1	19.5 ± 14.9	0.001
Body image	20.6 ± 25.1	25.4 ± 30.7	0.202
Sexual/vaginal functioning*	17.7 ± 20.9	32.3 ± 31.3	0.001
Single-item scales			
Lymphedema	26.7 ± 32.0	10.6 ± 24.2	<0.001
Peripheral neuropathy	16.0 ± 24.5	23.9 ± 33.7	0.037
Menopausal symptoms	27.3 ± 33.3	31.7 ± 31.5	0.350
Sexual worry†	14.5 ± 26.3	26.3 ± 33.8	0.004
Sexual activity	30.9 ± 27.0	21.7 ± 25.9	0.017
Sexual enjoyment*	64.4 ± 31.1	53.7 ± 36.2	0.089

RHL = radical hysterectomy with pelvic lymphadenectomy.
*Question(s) answered by 175 (RHL) and 31 (CRT) participants.
†Question answered by 257 (RHL) and 57 (CRT) participants.

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Derks et al. Int J Gynecol Cancer 2017 27(2)

Acute mucositis:

Vaginaal: isobetadine spoelingen/ gynodaktarin

Vulvair: gynodaktarin

Vaginale/vulvaire ulceraties:

Hyperbare zuurstoftherapie

100% O2 onder 2ATM

30-40 sessies van 1a2 uur

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The Assessment and Management of Sexual Difficulties after Treatment of Cervical and Endometrial Malignancies

I. D. White

Table 2 — Clinical interventions for treatment-induced sexual difficulties

Sexual difficulty	Clinical intervention
Loss of sexual desire	Hormone replacement therapy (systemic vs topical) + testosterone
Arousal difficulti	
Sexual pain	Vaginal lubricants
	Topical oestrogen
	Vaginal dilator therapy
	Advice about coital positions
	Psychosexual therapy
Secondary vaginismus	Vaginal dilator therapy
	Kegel exercises
	Psychosexual therapy
Orgasmic difficulties	Vibrator therapy
	Psychosexual therapy
Reduced sexual satisfaction	Psychosexual therapy
Sexual aversion	Psychosexual therapy

ONLY RANDOMIZED TRIAL !!!

Clinical Oncology, 2008

PREVENTIE

- Preventief dilateren
  - Zo geen partner
  - Pelot/staafje/vibrator
  - Verschillende maten
- Inbrengen tot cervix/vaginakoepel, 3x/week
- Zo vergroeiingen digitaal losmaken < 6 weken

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ERECTIELE DYSFUNCTIE BIJ DE MAN

Erectile dysfunction after prostate three-dimensional conformal radiation therapy

Correlation with the dose to the penile bulb

A. Magli[1] · M. Giangreco[2] · M. Crespi[3] · A. Negri[3] · T. Ceschia[1] · G. De Giorgi[4] · F. Titone[1] · G. Parisi[1] · S. Fongione[1]

Strahlenther Onkol 2012 · 188:997–1002

N= 19
3D-CRT to 72-76 Gy
No ADT

D_{mean} penile bulb <50 Gy

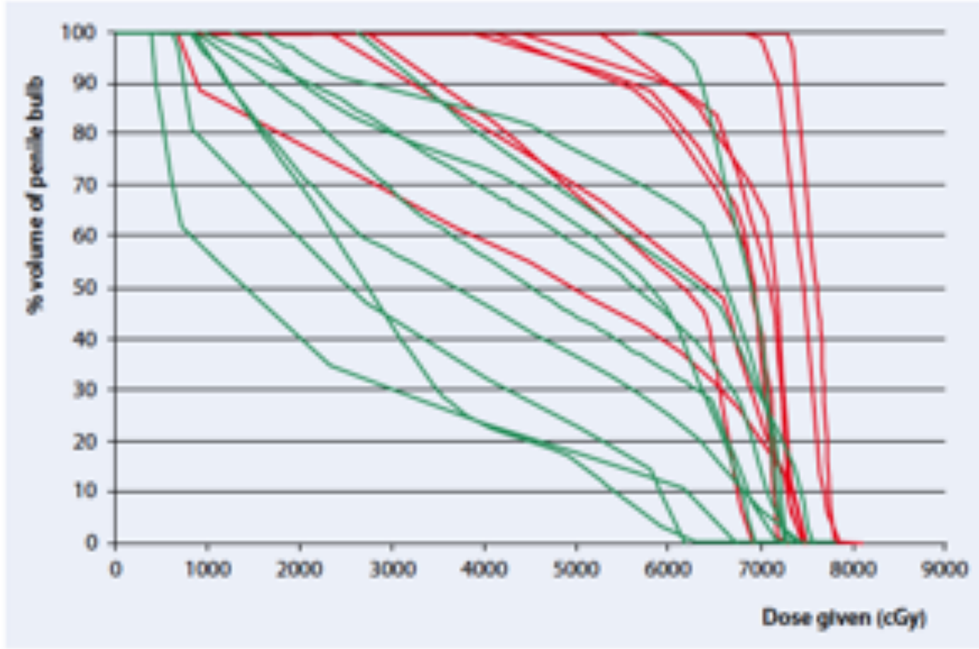

Fig. 1 ▲ Comparison of the dose–volume histograms of the penile bulb in potent (*green*) and impotent (*red*) patients

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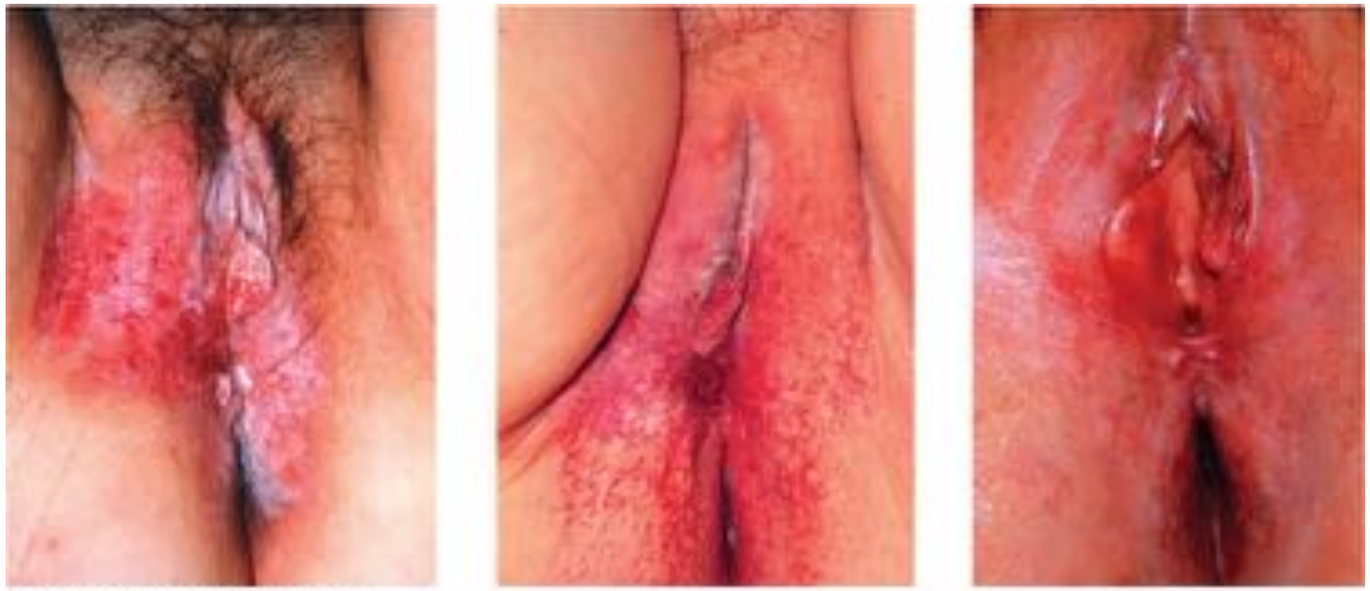
Therapie: sildenafil, tadalafil, vardenafil,…

ERYTHEEM

- Locatie: vulvair, anaal, bilnaad, liezen
- Risicofactoren:
  - Huidtype
  - Comorbiditeit: diabetes, hypertensie, lupus, reuma
  - Medicatie: bv cordarone
  - dosis
- Behandeling:
  - Wondzorg intacte huid
    - Hygiëne
    - Flamigel/zalven/cremes?
  - Vanaf G3 erytheem
    - Goed reinigen (thuisvpl?)
    - Siliconen/vetverband
    - Alginogel
  - Evtl RT onderbreken
  - AB of antifungica oraal IN



Textbook of gynaecologic oncology, Ayhan et al. 2013

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ERYTHEEM: PREVENTIE

- Gebruik douche-olie, geen bad, lauw water.
- Deppen
- Elektrisch scheren
- Katoenen kledij
- Geen kleefpleisters (wel bv mepitac)
- Preventie: Cavilon Advanced

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BOT/BEENMERG - TOXICITEIT

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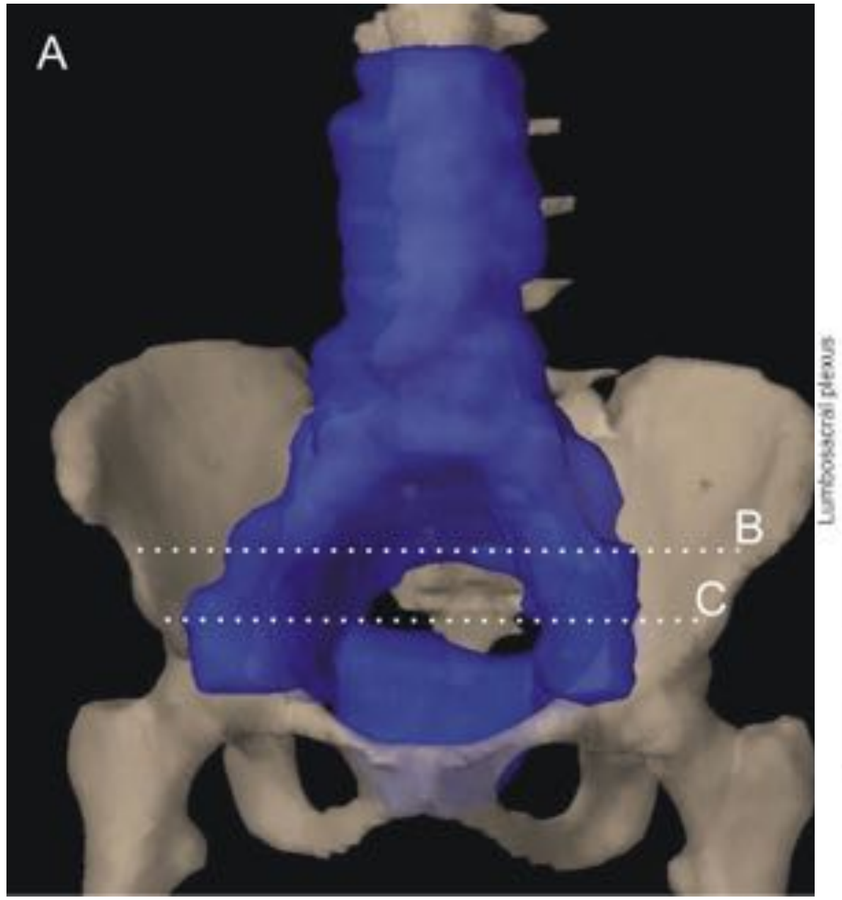
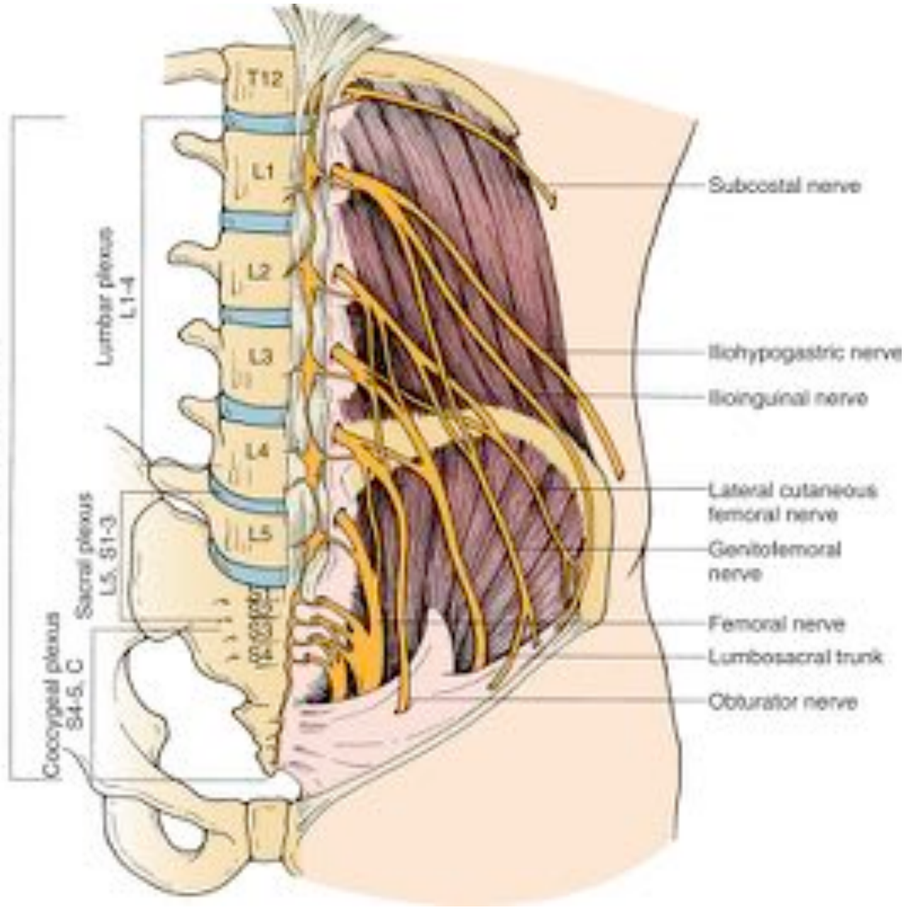
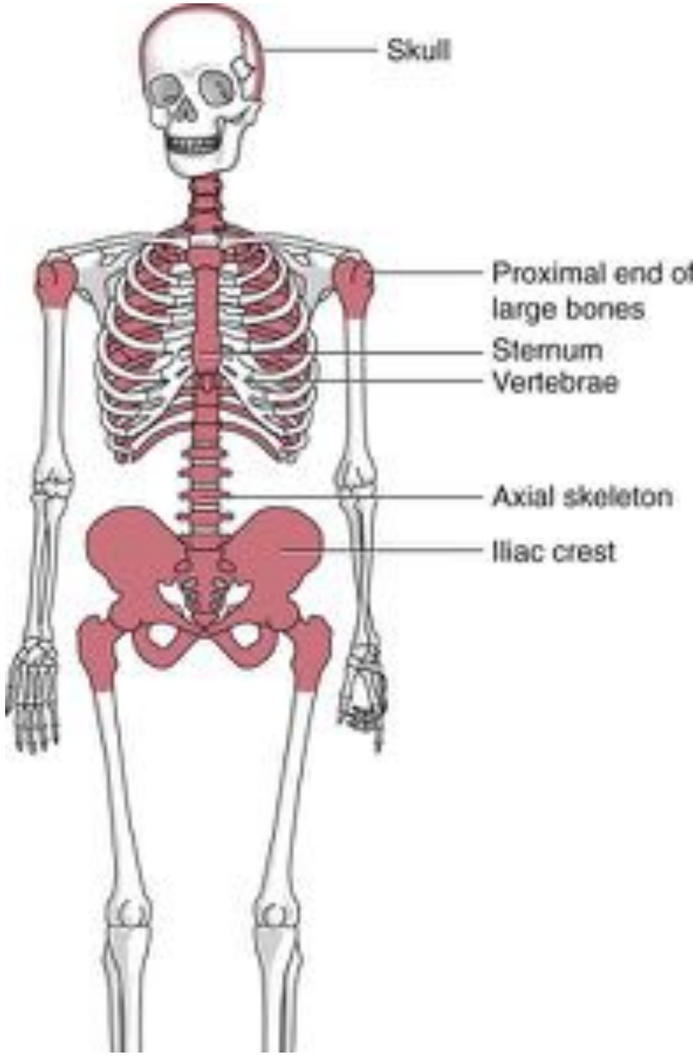


Insufficientie fractuur



Lumbosacral plexopathy



Bone Marrow Toxicity

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INSUFFICIENTIE FRACTUREN

- 3-45% van de bestraalde patienten
- Risicofactoren: vrouw, > 60j, <55kg, osteoporose, dosis (>45Gy)
- Timing: 14 tot 20 maand na einde RT, 85% < 2jr (zelden > 3j)
- Lokalisatie:
  - Vaak multifocaal, sacrum bijna altijd betrokken (vaak symmetrisch bil.)
  - Sacrum > acetabulum > ramus sup. pubis >ramus inf. pubis > femurkop
- Behandeling:
  - Verwijzing orthopedie: stabiel? restrictie activiteit noodzakelijk? HK-interventie noodzakelijk?
  - Pijncontrole
  - Nazicht/therapie vit D en osteoporose, evtl bisfosfonaten

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LUMBOSACRALE PLEXOPATHIE

- Zeer zeldzaam, 1-2/1000
- Risicofactoren: concurrente neurotoxische CT, DM, AHT, vasculaire collageenziekten, hyperlipidemie, dosis
- Timing: insidieus, chronisch, maanden tot jaren na RT, med. 5j (1-31j)
- Behandeling:
  - Uitsluiten tumoral invasie!!!
  - Pijncontrole: tricyclische antidepressiva, gabapentine, pregabaline, SSRIs

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HEMATOLOGISCHE TOXICITEIT

- Beenmergactiviteit:
  - 50-55% lumbosacraal, ilium, ischium, pubis en proximale femur
  - 25% in pelvis.
- Risicofactoren: geslacht, concomittante chemotherapie, leeftijd, dosis en bestraald volume.
- Preventie:
  - Aandacht voor dosisbeperking op bot/beenmerg!

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LYMPHOEDEEM

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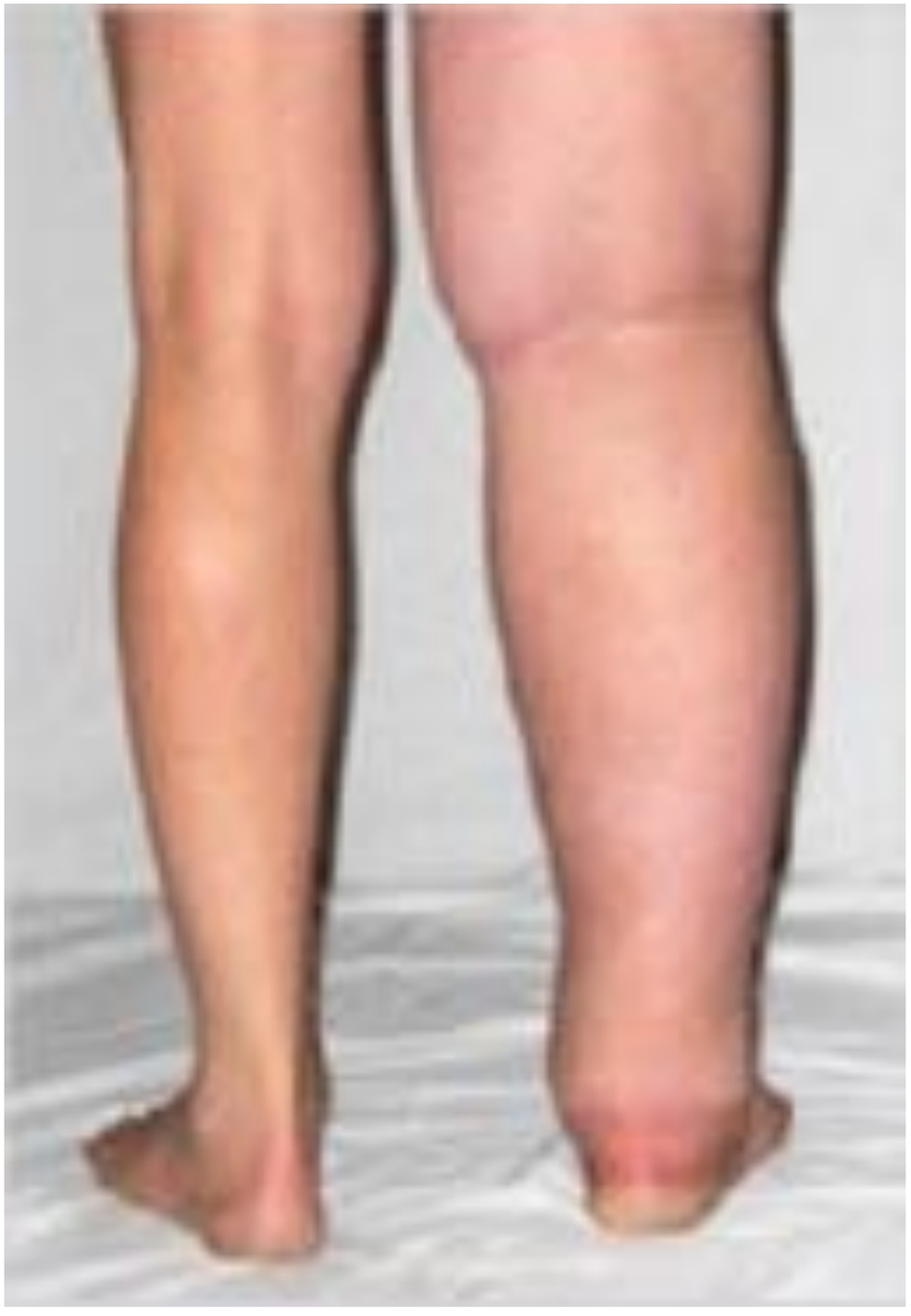

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ONCOLOGISCH LYMFOEDEEM

Incidentie

- Na **gynaecologische** ingreep: zeer variabel: beschreven van 1-73%[1]
  - Baarmoederhalskanker: 11-24%
  - Endometriumkanker: 1-47%
  - Ovariumkanker: 5-40%
  - Vulvakanker: 30-70%
- **Maligne melanoma**: na liesklieruitruiming: 26%
- Na **urologische** ingreep[2]
  - Peniskanker: 23-33%
  - Prostaat mét lymfeklierdissectie: 13%
  - Prostaat met radiotherapie: 9%
  - Robot-geassisteerde prostatectomie[3]: 20%

[1] BIGLIA, 2017, ANTICANCER RESEARCH
[2] ROCKSON, 2008, ANNALS OF THE NY ACADEMY OF SCIENCES
[3] RASKIN, 2018, JOURNAL OF UROLOGY

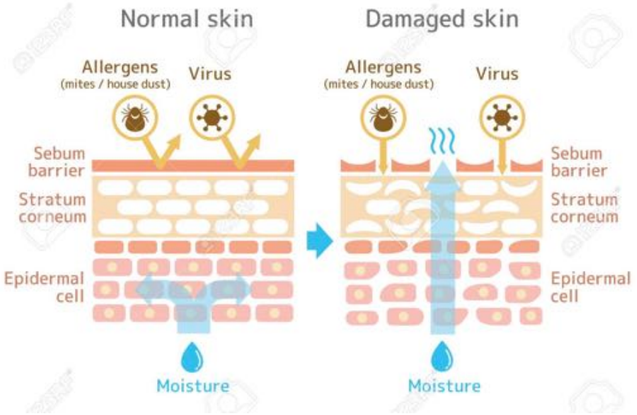
RISICOFACTOREN

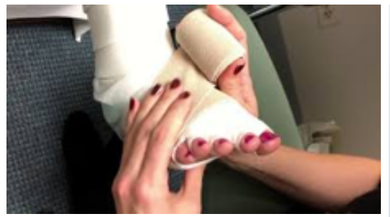
- Chirurgie[1]
  - Transectie van lymfebanen (regio en aantal belangrijk)
- Radiotherapie[2]
  - Acuut weefseloedeem → kan tijdelijk lymfoedeem veroorzaken
  - Fibrose van de lymfeklieren
  - Schade aan endotheliale cellen
  - Bacteriële kolonisatie met vrijzetting pro-inflammatoire cytokines door mono-nucleaire cellen
- Chemotherapie[3]
  - Taxanen: theorie: capillaire lek in combinatie met radiotherapie
- Genetische predispositie[4]: HGF/MET, Cx47…
- Hoge BMI
- Onvoldoende lichaamsactiviteit
- Congestief hartfalen, nierproblemen, overvloedige hydratatie (bvb. chemotherapie)
- Voorafbestaand lymfoedeem, veneuze problemen
- Infectie, wonde, insektebeten, allergische reactie…
- Hoge temperatuur (sauna, evenaarslanden), langdurige belasting…

[1] RIDNER, 2013, SEMINARS IN ONCOLOGY NURSING
[2] SONIS, 2004, SEM ONCOL NURS
[3] SHIH, 2009, JCO
[4] FINEGOLD, 2008, LYMPHAT RES BIOL

Conservatieve behandeling: Vier pijlers

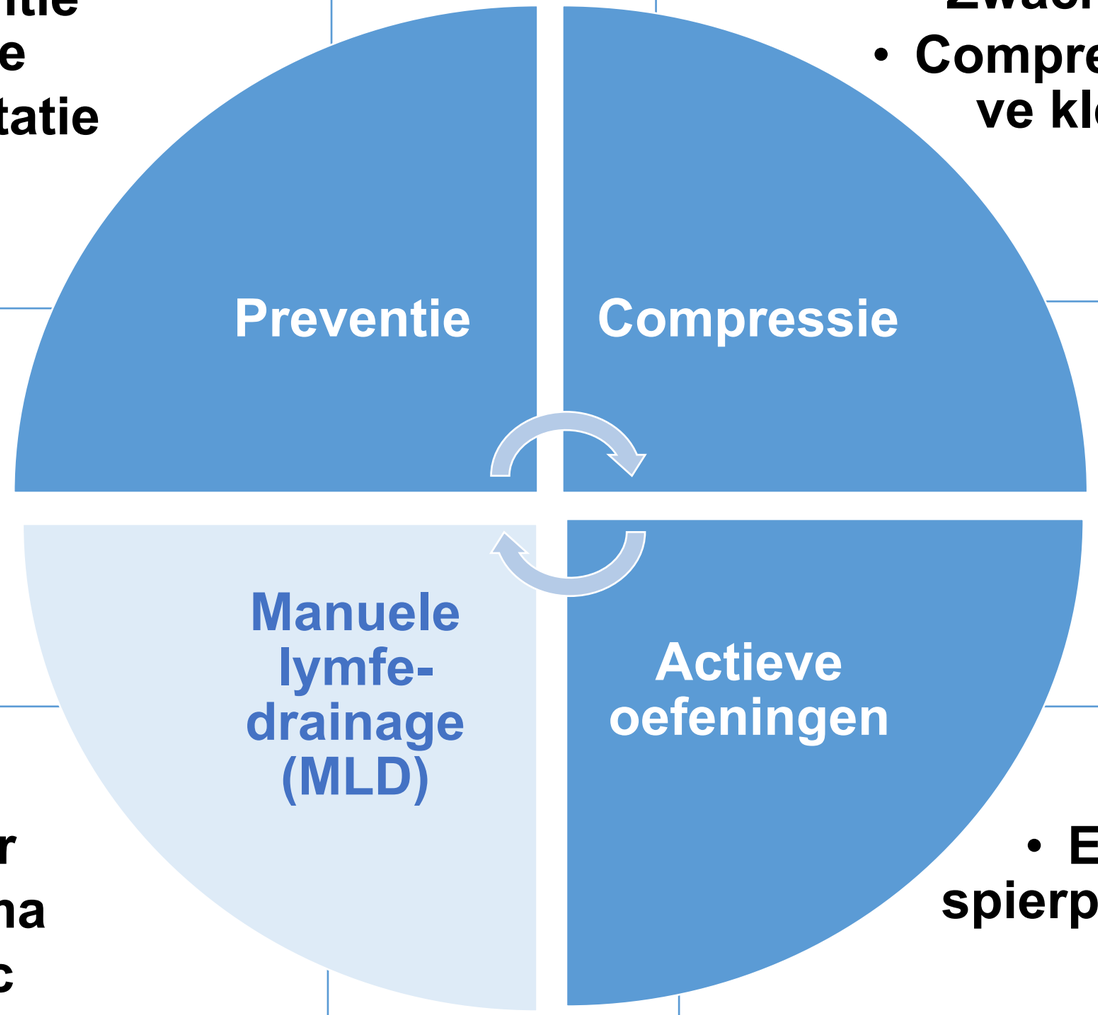
- Preventie infectie
- Hydratatie huid





- Zwachtelen
- Compressie-ve kleding

- Vodder
- Oedema
- Le Duc



- Eigen spierpomp

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