



Associazione Italiana
Radioterapia Oncologica
Gruppo Interregionale
Lazio/Abruzzo/Molise

Le terapie di supporto in Radioterapia:

Verso una Guida Pratica

Lunedì 4 Dicembre 2017
Centro Studi Cardello
Via del Cardello 24 – Roma

VULVITI E VAGINITI

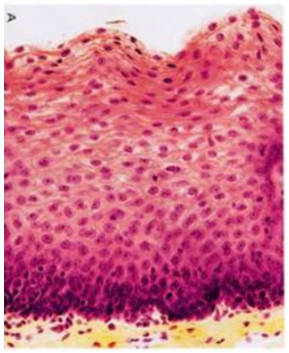
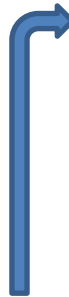
Cenni di patogenesi e strumenti di valutazione

G. Macchia

Presidi di prevenzione e trattamento delle tossicità

E. Ippolito

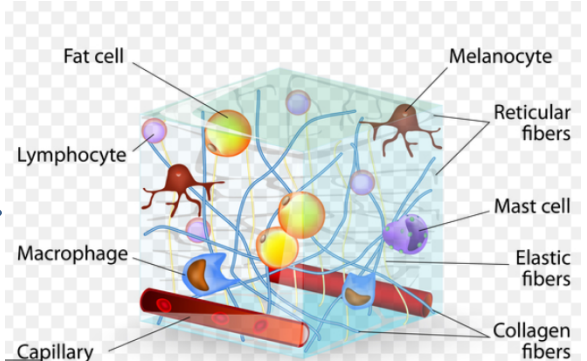
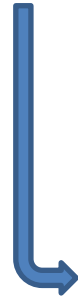
Pathogenesis: acute damage



vaginal damage on epithelial layers with **cell necrosis** and **proliferation blockage**

damaged epithelium easily breaks down

more easily attacked by microorganisms, with increased vaginitis.



obliteration of the blood vessels that interfere with physiological vaginal lubrication

marked inflammatory infiltrate



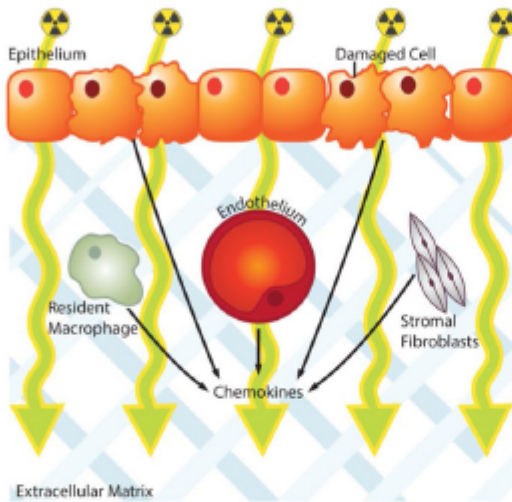
slim mucosa unable to produce glycogen

→ vaginal flora modification (reduction or disappearance of lactobacilli)

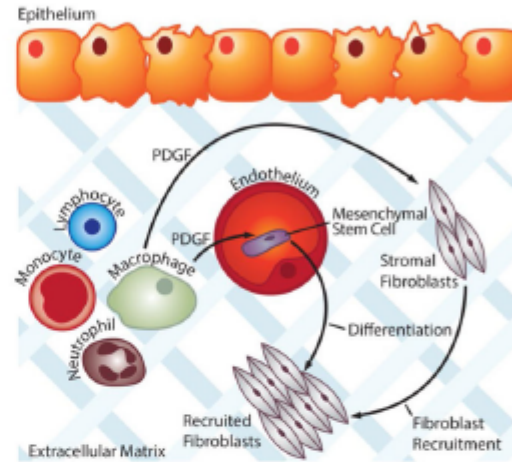
→ postmenopause like status

Schematic depicting four broad stages in the pathogenesis of RIF

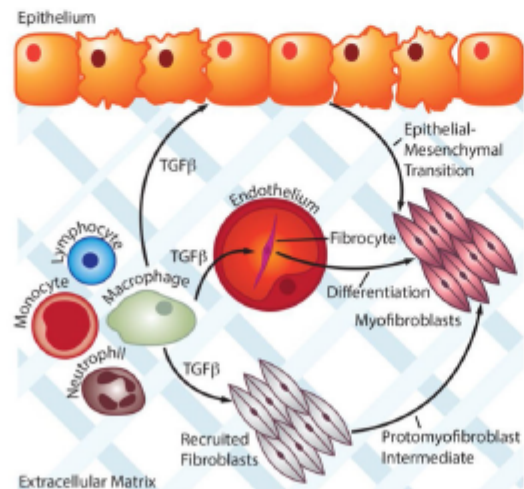
① Initial Injury



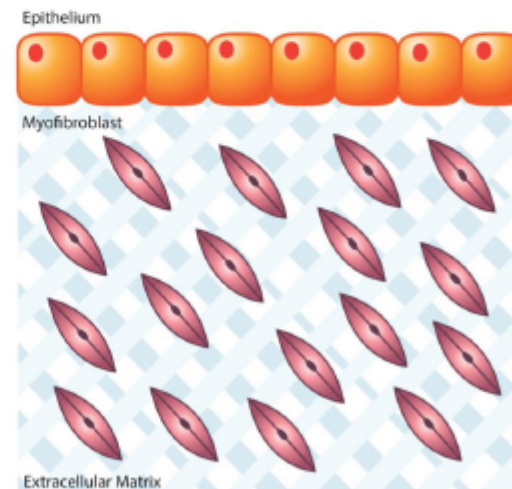
② Inflammation & Fibroblast Recruitment



③ Myofibroblast Production



④ ECM Deposition



1 **Ionizing radiation** damages cells
→ production of **proinflammatory cytokines**.

2 **Neutrophils, lymphocytes, and monocytes** arrive at the site of injury while resultant M2 **macrophages** produce **PDGF**,
→recruitment of stromal **fibroblasts**

3 Subsequent **TGF-β production** by M2 macrophages promotes the development of **myofibroblasts** from recruited stromal fibroblasts through a protomyofibroblast intermediate as well as through epithelial–mesenchymal transition and differentiation of circulating fibrocytes

4 Over time, **myofibroblast proliferation** along with excess deposition and **decreased degradation of extracellular matrix** leads to **fibrosis** with **reduced vascularity and a paucity of cells**

The “classic” morbidity grading system

LENT-SOMA

Late Effects in Normal Tissues—Subjective, Objective, Management and Analytic scales

**Perez CA,
1993**

FRANCO- ITALIAN GLOSSARY

Reporting gynaecological cancer morbidity regardless of the treatment used

**Chassagne
D.
1988→1993**

RTOG-EORTC

Late Radiation Morbidity Scoring Schema of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer

**Pavy JJ,
1995**

CTC-AE v4.03

NCI Common Terminology Criteria for Adverse Events

**NCI
2003**

FRANCO-ITALIAN GLOSSARY

Endpoint	G1	G2	G3
Franco-Italian Glossary			
Vaginitis	Acute symptoms of vulvovaginitis interrupting the treatment for more than 10% of the planned overall treatment time or lasting more than 2 weeks after the completion of treatment	Repeated infectious vaginitis	Death due to complication
Stenosis	Vaginal narrowing and/or shortening to 1/2 or <1/2 of the original dimensions	Vaginal narrowing and/or shortening to more than 1/2 of the original dimensions	Death due to complication
Dyspareunia	Mild dyspareunia	Moderate dyspareunia	Death due to complication
Edema/telangiectasia	Asymptomatic vaginal or vulvar edema with or without telangiectasia	Symptomatic vaginal or vulvar edema with or without telangiectasia requiring treatment	Death due to complication
Perforation/tear	Uterine perforation or pyometra not requiring treatment	Uterine perforation or pyometra requiring treatment	Death due to complication
Rectum			Rectovaginal fistula
Bladder and urethra		Early postoperative vesicovaginal fistula with complete healing and normal function after treatment	Early or late vesicovaginal fistula with permanent anatomical and/or functional damage

In respect to LENT-SOMA may underestimate treatment morbidity from the patient's perspective

Chassagne D, Sismondi P, Horiot JC et al (1993) A glossary for reporting complications in the treatment of gynecologic cancers. *Radiother Oncol* 26:195–202

RTOG ACUTE Radiation Morbidity

Tissue	Grade 1	2
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema
Mucous membrane	Irritation / may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia
	3	4
	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis

Perez CA, Brady LW (1993) Late radiation morbidity scoring criteria (RTOG, EORTC). In: Perez CA, Brady LW (eds) Principles and practice of radiation oncology, 2nd edn. Lippincott, Philadelphia, pp 53–55

Vaginal inflammation

G1

Mild discomfort or pain, edema, or redness

G2

Moderate discomfort or pain, edema, or redness; limiting instrumental ADL

G3

Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration

G4

Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated

G5

Death

Grade 1

RTOG

Tissue	Grade 1
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating
Mucous membrane	Irritation / may experience mild pain not requiring analgesic

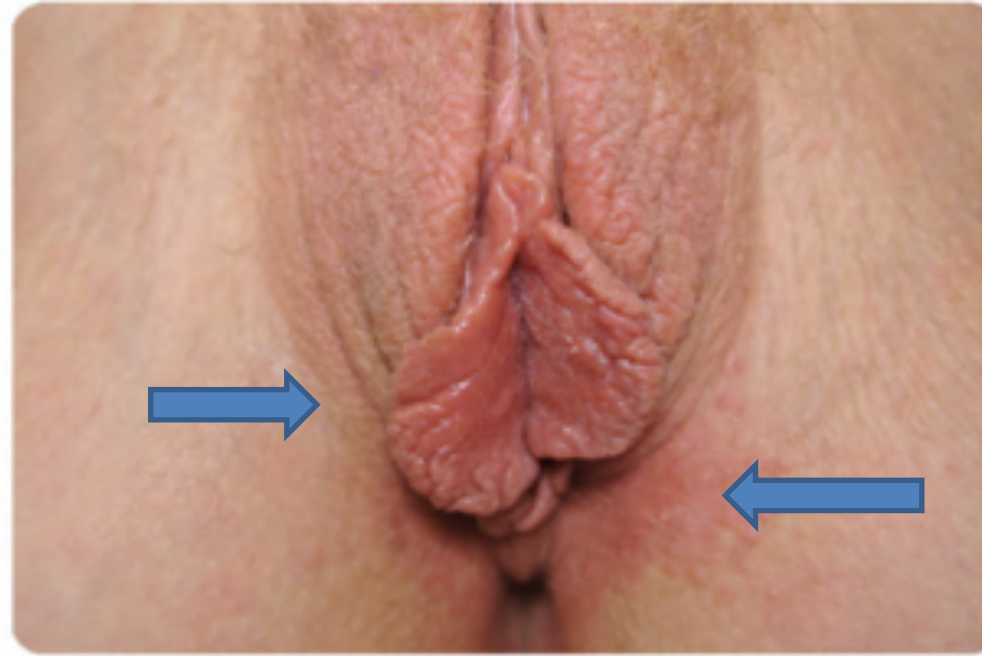
CTCAE v4.0

Mild discomfort or pain, edema, or redness

Figure 13.23 B - Substantial erythema affecting the vestibule.



Figure 13.23 A - Substantial edema of the labia minora.



Grado 2

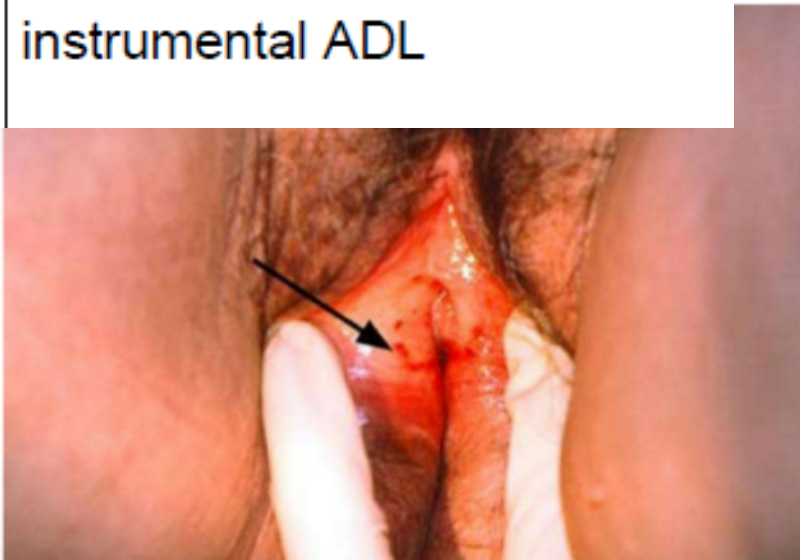
RTOG

Tissue	2
Skin	Tender or bright erythema, patchy moist desquamation / moderate edema
Mucous membrane	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia

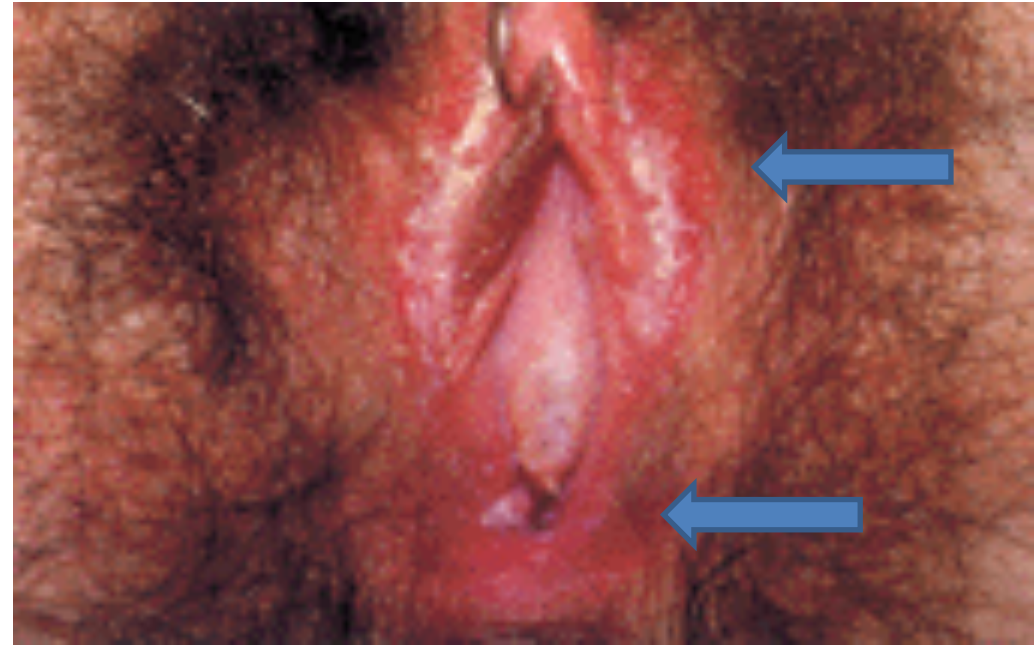
CTCAE v4.0

Moderate discomfort or pain, edema, or redness; limiting instrumental ADL

Figure 13.24 - Edema of the labia minora with thin superficial vesiculation (humid eczema).



Desquamative inflammatory vaginitis.



Vulvodynia Assessment

Step 1 - Visual Examination

37



Patient #1
Severe Erythema



Patient #2
Moderate Erythema



Patient #3
Minimal Erythema / Severe Pain

Pain severity and subsurface inflammation do not consistently correlate with the amount of erythema observed. (Bergeron 2001, Farage 2009)

GRADE 3

RTOG

Tissue	3
Skin	Confluent, moist desquamation other than skin folds, pitting edema
Mucous membrane	Confluent fibrinous mucositis / may include severe pain requiring narcotic

CTCAE v4.0

Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration



GRADE 4

RTOG

Tissue	4
Skin	Ulceration, hemorrhage, necrosis
Mucous membrane	Ulceration, hemorrhage or necrosis

CTCAE v4.0

Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated



Figure 3. Acute radiation dermatitis affecting the groins, vulva, perineum and inner thighs. There is superficial ulceration of the left groin. Such an extensive reaction is uncommon but is associated with interruption of treatment.

Late toxicities

Pigmentation changes

Hair loss (permanent)

Telangiectasia

Atrophy

Ulceration

Fibrous changes

Changes in the **microvasculature**, with loss of capillaries and impaired microcirculation, result in secondary mucosal atrophy.

Pathological dilation of capillaries results in **telangiectasias**, which are prone to **bleeding**.

Increased collagen production within the fibroconnective tissue can lead to **shortening and tightening of the vagina**. Eventually, ulceration, necrosis, and fistulae can develop

Treatment-related **loss of ovarian function** and consequent hormonal insufficiencies can augment the mucosal alterations and can also cause **menopausal** changes in premenopausal women .

Vulval craurosis

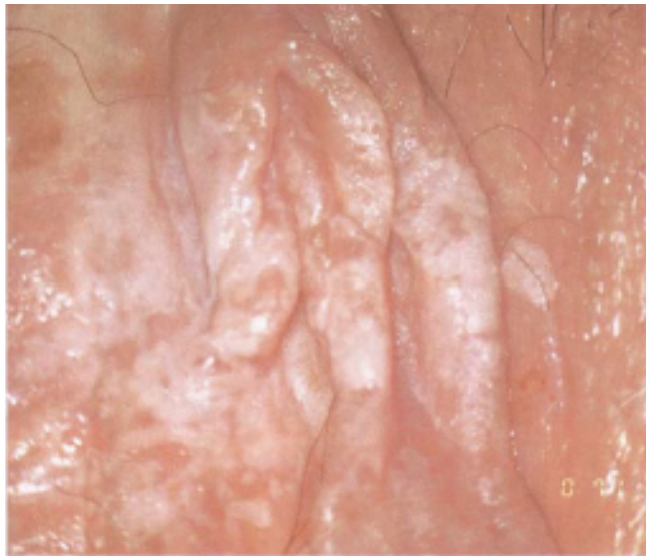


Fig. 9.33 An extensive area of hyperkeratotic white tissue involving the periclitoral area, labia majora, and labia minora. A large excision procedure was carried out and a small focus of early invasive carcinoma (<1 mm) was found in the periclitoral area.

Lichen Sclerosus



Image courtesy of Dr. Libby Edwards



Image courtesy of Dr. Andrew Goldstein

For information on diagnosis and treatment, see Chi 2012, Moyal-Barracco 2014.

Lichen sclerosus (LS) is a chronic inflammatory condition of the vulva, most likely of autoimmune etiology. Both photos show cases of LS, but the photo on the left shows a severe case with a whitish color, itching, and fragile skin that may bruise or tear with contact or sexual intercourse. Diagnosis should be confirmed with vulvar skin biopsy evaluated by a dermatopathologist prior to initiating treatment with ultra-potent topical corticosteroids.

Effects of Reinitiating Topical Estrogen Therapy



•Patient image represents the atrophic appearance several years after menopause and reveals the inflammatory changes and shrinkage.



•Patient image represents the "normalization" of the appearance after 3 months of topical estrogen therapy.



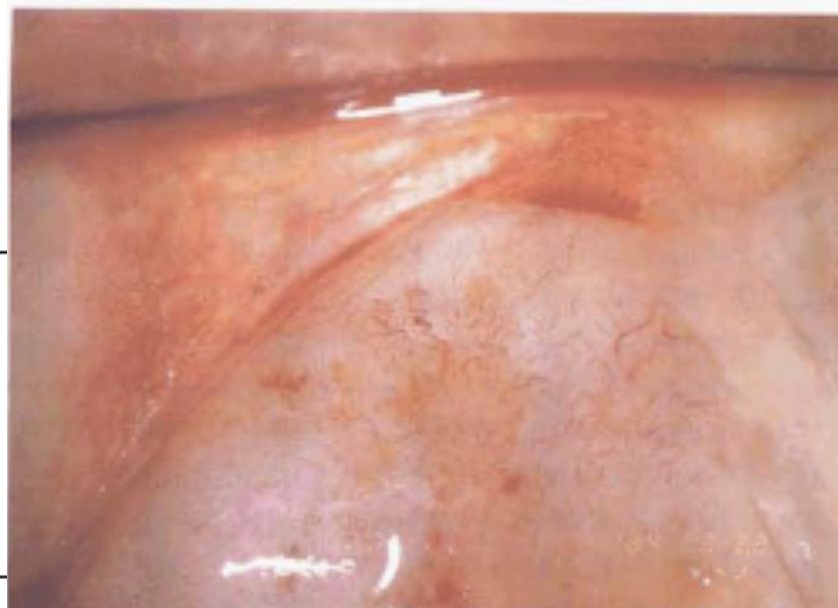
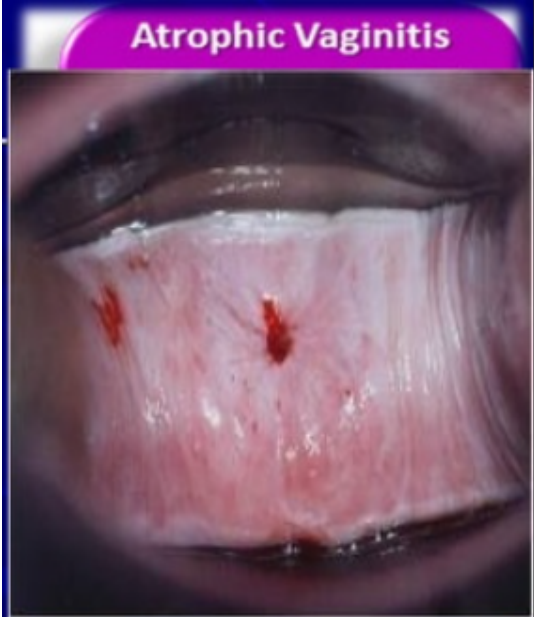
Contact dermatitis

Often in follow-up especially if incontinence & diabetes



Consequential late radiation dermatitis with chronic telangiectasia, ulcer, and exposed bone.

	Vaginal stenosis	Vaginal dryness
G1	Vaginal narrowing and/or shortening not interfering with function	Mild
G2	Vaginal narrowing and/or shortening interfering with function	Interfering with sexual function; dyspareunia; intervention indicated
G3	Complete obliteration; not surgically correctable	N.A.
G4	N.A.	N.A.
G5	N.A.	N.A.



the vaginal vault after irradiation for cervical carcinoma in a postmenopausal woman:

- thin white epithelium
- vessels with irregularity in caliber and branching (not unlike those seen in invasive cancer)
- vasculature extremely vulnerable to any trauma

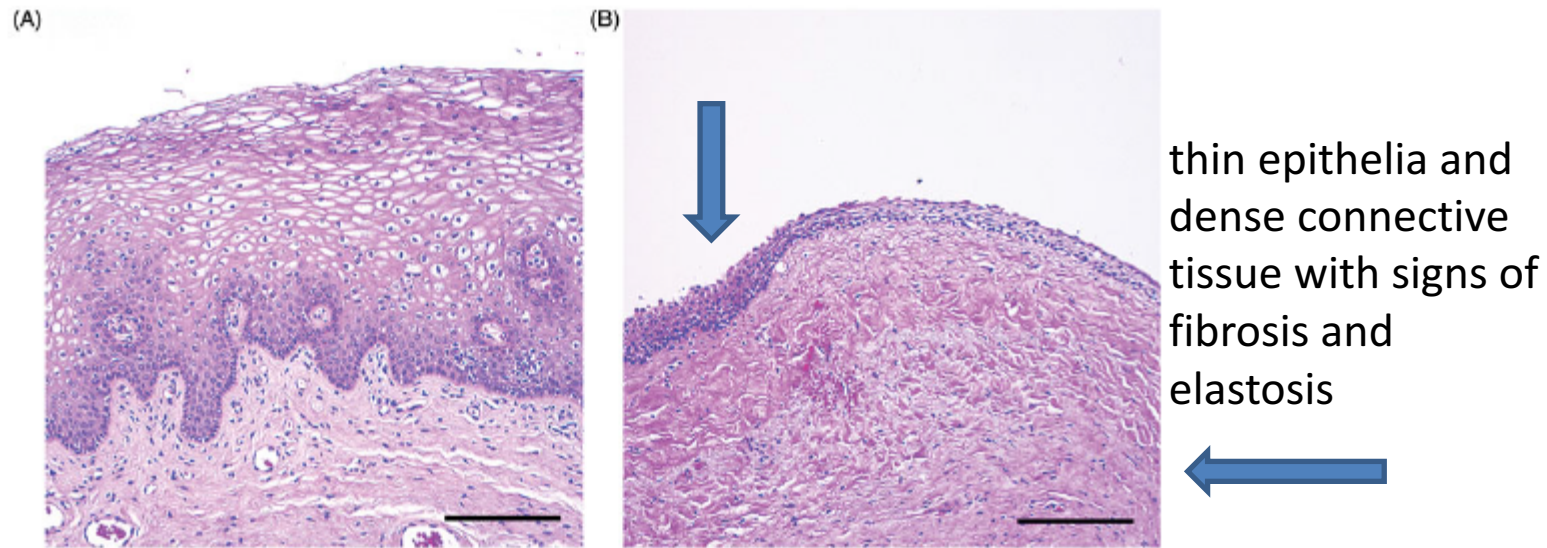


Figure 1. Hematoxylin-eosin stained biopsies from the vaginal wall in healthy women with thick squamous cell epithelium with dermal papillae (A), and cervical cancer survivors with thin epithelium and dense connective tissue with signs of fibrosis and elastosis (B). Scale bar = 200 μ m.

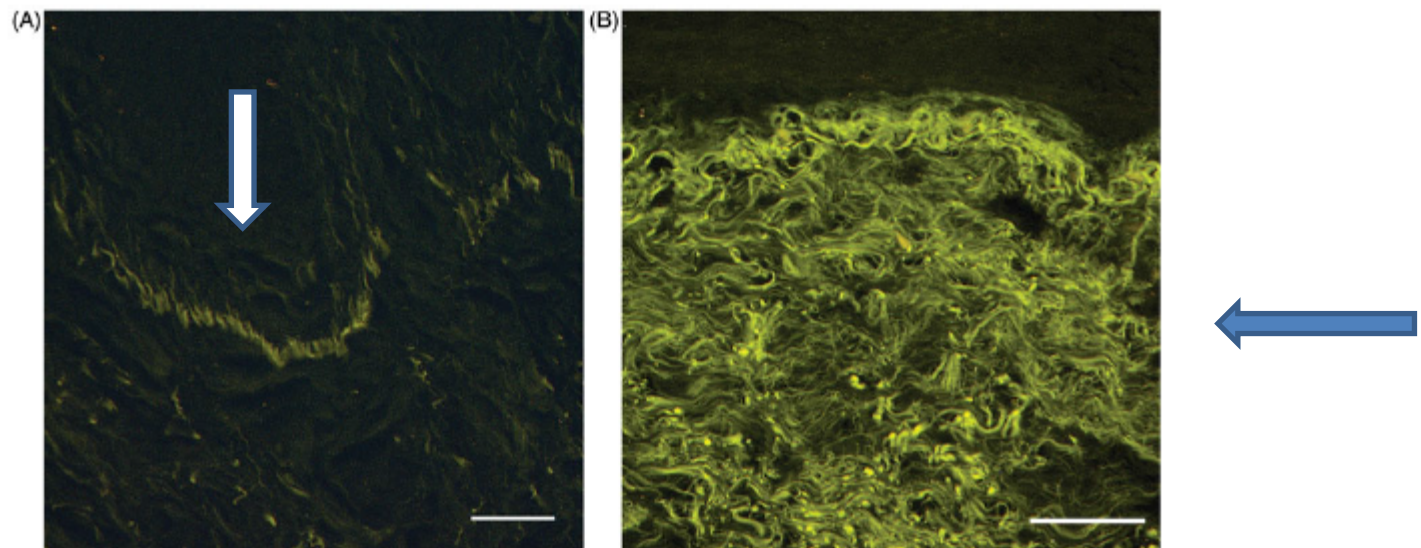


Figure 2. Autofluorescent elastin fibers under the basal membrane in the vaginal wall in healthy women (A), and thick aggregated elastin fibers scattered throughout the connective tissue in the cervical cancer survivors (B). Scale bar = 200 μ m.

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Radiation-induced morphological changes in the vagina

Conclusions:....the classic radiation morbidity grading scales are not concise in their reporting. ...**Vaginoscopy** is an easily applicable, informative, and well-tolerated procedure **for the objective assessment of morphological vaginal changes after radio(chemo)therapy** and provides comprehensive and detailed information. This allows for **precise classification of the severity of individual changes.**

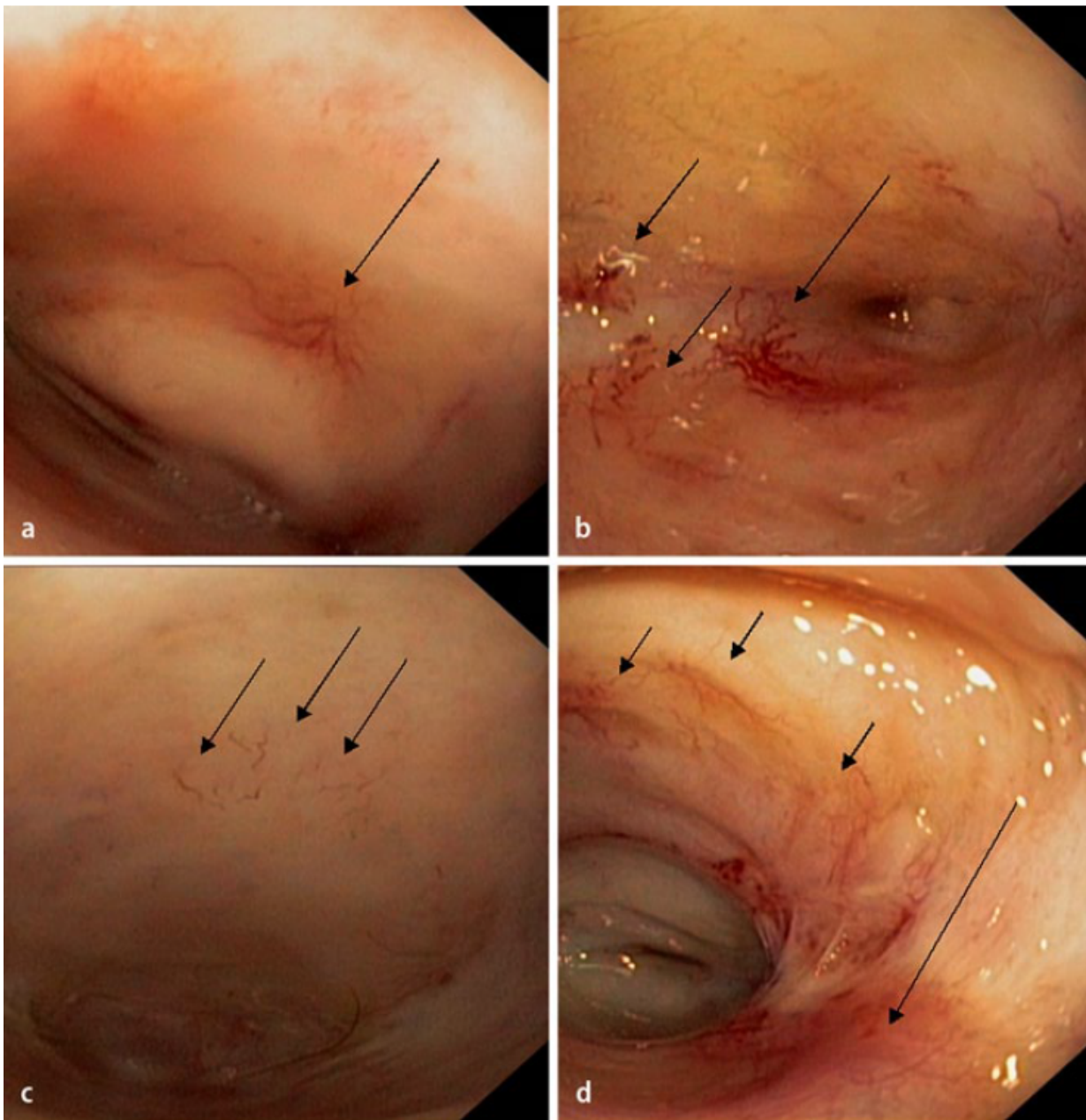


Fig. 2 ▲ Telangiectasia (TA). **a** Up to 2 TA/cm² in a single area (G1). **b** 3–4 TA/cm² in a single area (G2). **c** 3–4 TA/cm² in a single area (G2). **d** Any number of TA present in multiple areas

**K. Kirchheiner et al.
Radiation-induced
morphological changes in
the vagina Strahlentherapie
und Onkologie 11 · 2012**

Clinical Investigation: Gynecologic Tumor

Manifestation Pattern of Early-Late Vaginal Morbidity After Definitive Radiation (Chemo)Therapy and Image-Guided Adaptive Brachytherapy for Locally Advanced Cervical Cancer: An Analysis From the EMBRACE Study

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Jacob C. Lindegaard, MD, DMSc,[§] Henrike Westerveld, MD, PhD,^{||}
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and Richard Pötter, MD, PhD^{*,†}

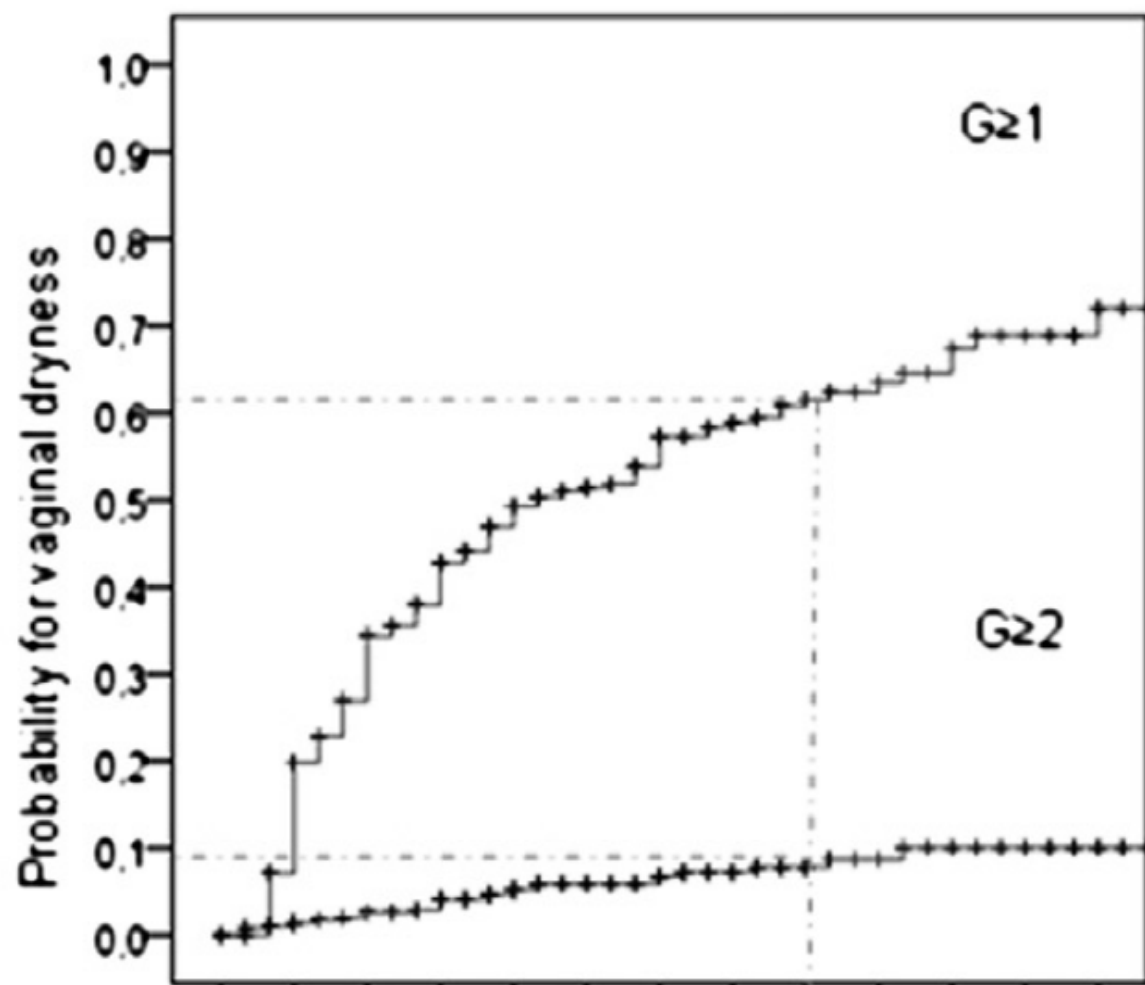
Supplemental material: Vaginal morbidity grading CTCAE v3.0

	Vaginal stenosis	Vaginal dryness	Vaginal mucositis	Vaginal bleeding (Hemorrhage, GU)	Vaginal fistula
G1	Vaginal narrowing and/or shortening not interfering with function	Mild	Erythema of the mucosa; minimal symptoms	Minimal or microscopic bleeding; intervention not indicated	Asymptomatic, radiographic findings only
G2	Vaginal narrowing and/or shortening	Interfering with sexual function; dyspareunia;	Patchy ulcerations; moderate symptoms or	Gross bleeding, medical intervention, or	Symptomatic; noninvasive intervention

Results: At 2 years, the actuarial probability of severe vaginal morbidity (grade ≥ 3) was 3.6%. However, mild and moderate vaginal symptoms were still pronounced (grade ≥ 1 , 89%; grade ≥ 2 , 29%), of which the majority developed within 6 months. Stenosis was most frequently observed, followed by vaginal dryness. Vaginal bleeding and mucositis were mainly mild and infrequently reported.

G4	N.A.	N.A.	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Life-threatening consequences; major urgent intervention indicated	Life-threatening consequences; operative intervention requiring partial or full organ resection; permanent urinary diversion
G5	N.A.	N.A.	N.A.	Death	Death

Abbreviations: G=grade, N.A.=not applicable



0	6	12	18	24	30	36
588	342	177	106	52	24	9
588	464	330	223	125	57	24

months after end of treatment
 patients at risk for any G21
 patients at risk for any G22

For Clinical Trial Use.....

Quality of Life Questionnaire Core-30 (QLQ-C30) 3.0

qualità della
vita in
generale

The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function

R. Rosen, C. Brown, J. Heiman, S. Leiblum, C. Meston, R. Shabsigh, D.
Ferguson, R. D'Agostino

www.nva.org/tools

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Ferguson, R. D'Agostino (2000) The Female Sexual Function Index (FSFI): A Multidimensional
Self-Report Instrument for the Assessment of Female Sexual Function, Journal of Sex & Marital
Therapy, 26:2, 191-208, DOI: [10.1080/009262300278597](https://doi.org/10.1080/009262300278597)

FACT-V (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>ADDITIONAL CONCERNS</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
V1	I am bothered by discharge or bleeding from my vulva	0	1	2	3	4
V2	I am bothered by odor coming from my vulva	0	1	2	3	4
Cx3	I am afraid to have sex	0	1	2	3	4
V3	I am bothered by swelling/fluid in my legs	0	1	2	3	4
Cx4	My vagina feels too narrow or short	0	1	2	3	4
V4	I am bothered by discomfort in my groin or legs.....	0	1	2	3	4

Janda M, I J Gynecol Cancer 2004 9, 14, 5: 875–881