



Genova, 19-22 novembre 2011
Porto Antico di Genova
Centro Congressi



Associazione
Italiana
Radioterapia
Oncologica

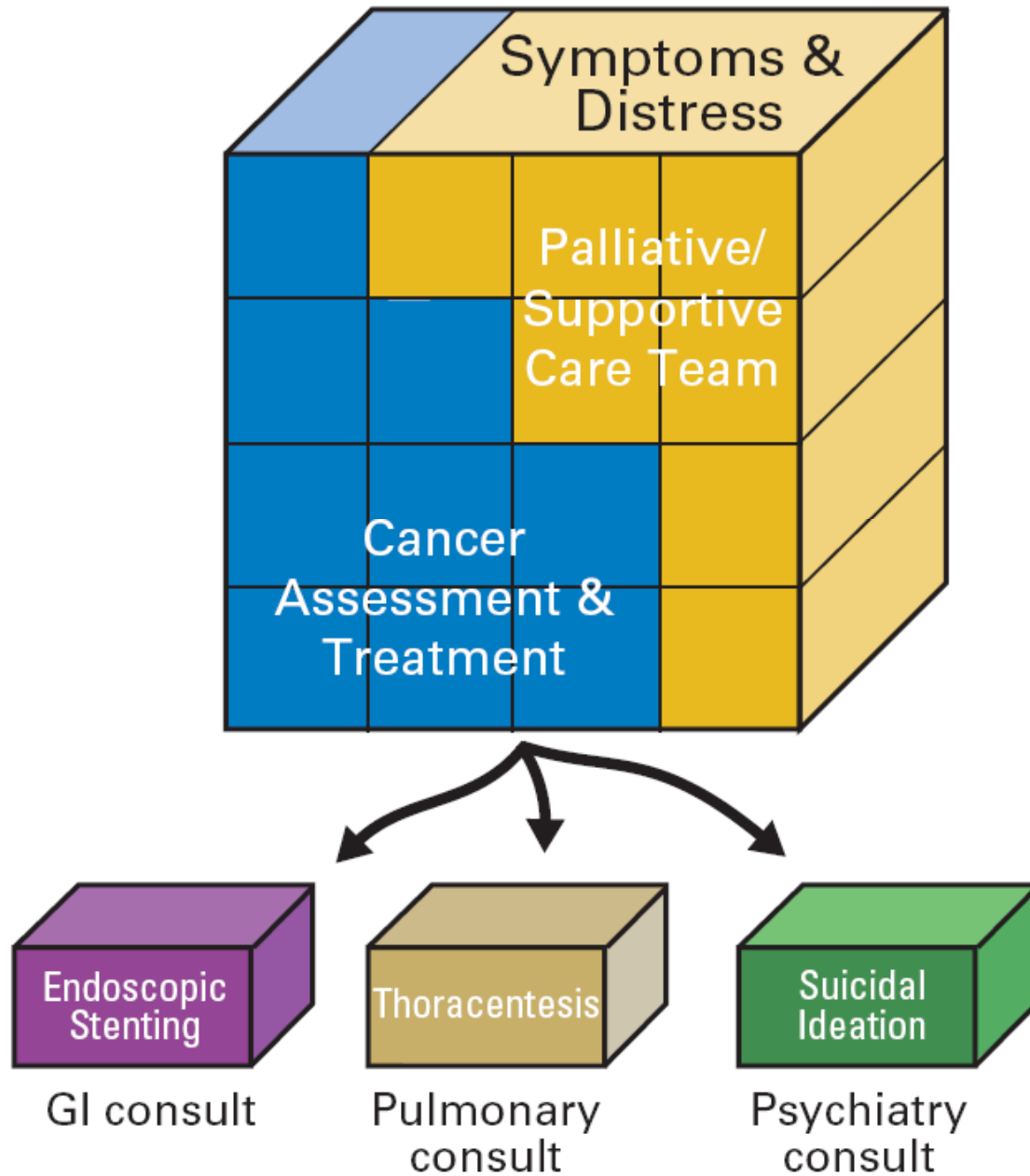
Radioterapia nelle neoplasie pelviche: tossicità e terapie di supporto

P. Ciammella

Supportive Care Makes Excellent Cancer Care Possible

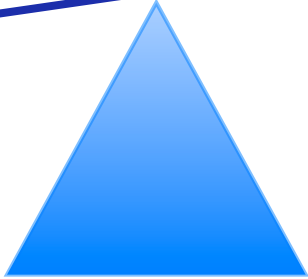
...is the prevention and management of the adverse effects of cancer and its treatment. This includes the management of physical and psychological symptoms and side effects along the continuum of cancer experience from diagnosis through anti-cancer treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship and end of life care are integral to supportive care

Integrated Care Model



Therapeutic effectiveness

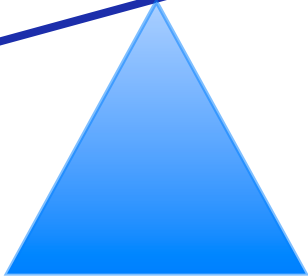
Toxicity



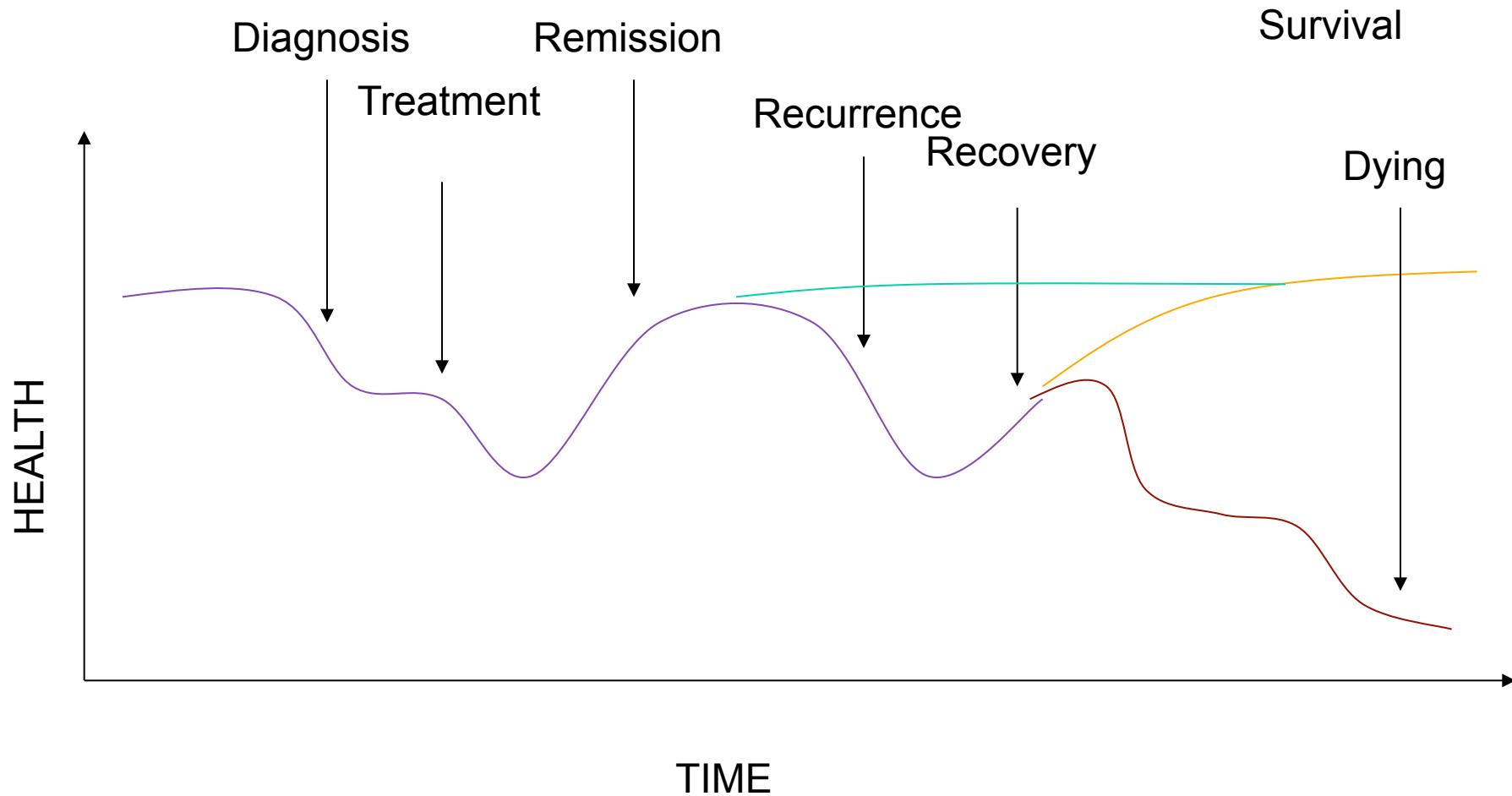
Current clinical research

Therapeutic effectiveness

Toxicity



The Cancer Trajectory



List of common cancers treated with radiotherapy

Common cancers curable at early stages with radiotherapy alone:

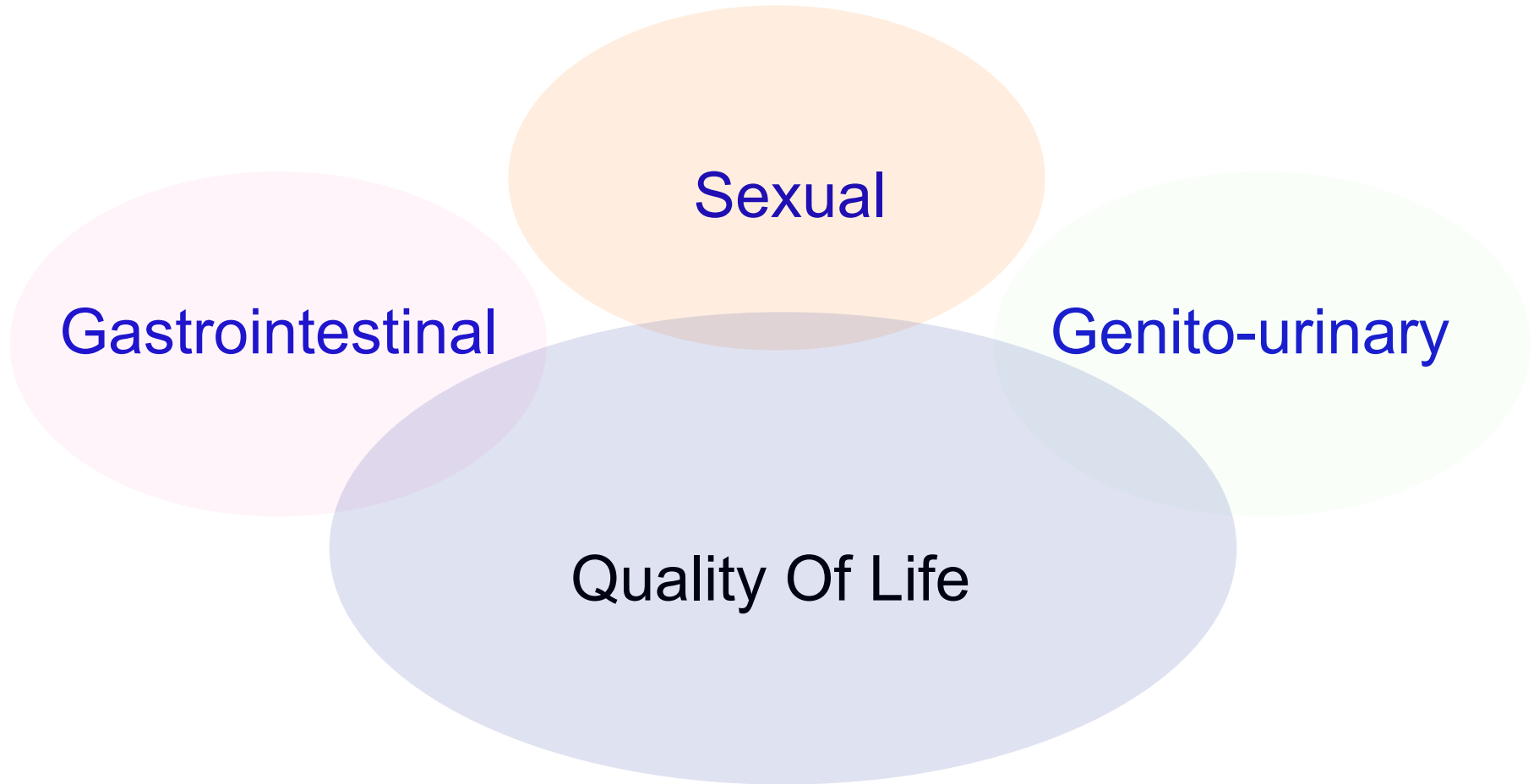
- Prostate carcinomas
- Head & neck carcinomas
- Non-small cell lung carcinomas
- Squamous and basal cell skin cancers
- Hodgkin lymphomas
- Uterine cervix carcinomas

Additional common cancers curable with regimens that include radiotherapy:

- Breast carcinomas
- Locally advanced lung carcinomas
(non-small cell and small cell)
- Seminomas
- Endometrial carcinomas
- Locally advanced uterine cervix
- Several CNS tumors
(e.g., ependymoma, glioma)
- Soft tissue sarcomas
- Rectal and anal carcinomas
- Lymphomas (Hodgkin and non-Hodgkin)
- Advanced head & neck carcinomas
- Bladder carcinomas
- Numerous pediatric malignancies
(e.g., Wilms tumor, medulloblastoma, neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma)

300 000 patients per year undergo pelvic radiotherapy worldwide

Pelvic radiation therapy



Sexual

Gastrointestinal

Genito-urinary

Quality Of Life

2007

Gastrointestinal Problems after Pelvic Radiotherapy: the Past, the Present and the Future

H. J. N. Andreyev

- Nine out of 10 will develop a permanent change in their bowel habit as a result
- Five out of 10 of all patients will say that this change in their bowel habit affects quality of life and two to three out of 10 will say that this effect on quality of life is moderate or severe
- Between one in 10 and one in 20 patients will develop very serious complications within the first 10 years after treatment
- It is estimated that severe gastrointestinal (GI) toxicity, i.e. fistulation, transfusion-dependent bleeding, stricture formation and secondary cancers, occurs in 5% of patients at 10 years

Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer

- ▶ There has been a threefold increase in the numbers of survivors of cancer in the last 30 years
- ▶ Chronic gastrointestinal side effects are a common cause of morbidity and reduced quality of life
- ▶ Side effects of treatment are frequently missed or overlooked because the current priority of cancer follow-up is to perform surveillance for recurrent cancer
- ▶ Individual GPs are unlikely to have many patients with complex problems after cancer therapy and so will require guidance if these patients are to be optimally managed
- ▶ Symptoms can often be alleviated or cured.

Prevention and treatment of the physical late effects from pelvic RT is an important goal for the individual patient with pelvic cancer

- ▶ Symptoms can often be alleviated or cured.

Rate and nature of chronic gastrointestinal problems after cancer treatment in patients at different tumour sites

Cancer site	Numbers undergoing treatment with curative intent	Treatment modalities	Survival at 5 years	Percentage affected by chronic symptoms affecting QoL	Type of chronic GI symptoms
Colorectal	90%	Chemotherapy Radiotherapy Surgery	60%	Colonic surgery: 15% Rectal surgery: 33% Short-course RT 66% Chemo-RT + surgery 50%	Bleeding Diarrhoea Frequency Incontinence Tenesums Urgency
Anal	80%	Chemoradiation	40-70%	N/A	Bleeding Frequency Incontinence Urgency
Gynaecological	90%	Surgery Radiotherapy Chemotherapy	Variable depending on tumour type	40% after treatment which includes RT	Bleeding Diarrhoea Flatulence Frequency Incontinence Malabsorption Pain Urgency
Urological	80%	Chemotherapy Radiotherapy Surgery	75%	30% after RT	Bleeding Constipation Diarrhoea Flatulence Frequency Incontinence Malabsorption Pain Urgency

Presentation of gastrointestinal side effects: acute, subacute or chronic

- Acute changes in gastrointestinal physiology can occur in any part of the gastrointestinal tract that is exposed to radiotherapy
- Some changes may lead to clinical symptoms; others remain subclinical
- Symptoms tend to start during the second week of treatment (when histological change is probably at a maximum) and peak by the fourth to fifth week (when histological changes are stable or improving)
- Chronic radiation-induced toxic effects are substantially more common than generally recognised
- 90% of patient given pelvic radiotherapy may develop a permanent change in their bowel habit after treatment

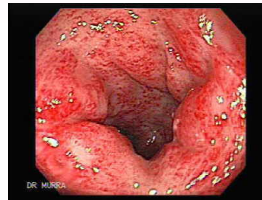
Scenario of bowel problems after pelvic RT

Enteritis

Proctitis



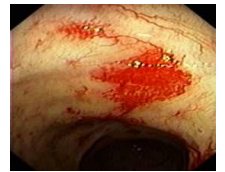
Appearance of symptoms



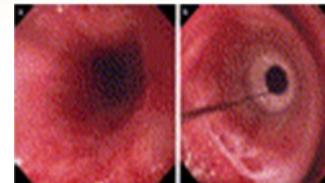
Peack of symptoms

1 week 2 week 3 week 4 week 5 week

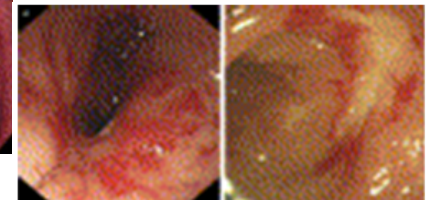
Early effects



Rectal ulceration



Rectal stricture



Erytaema and mild rectal stenosis

3 months

30 years

Late effects

Causes and management of symptoms

Causes	Incidence	Diagnosis	Therapy
Diarrhoea			
Bacterial overgrowth	25% in acute, 4-45% in chronic phase	Breath test, direct culture of small-bowel contents	Antibiotics with GRAM-negative activity Off-label treatment: probiotics, prebiotics, promotility agents
Bile-salt malabsorption	50% in acute, 50-83% in chronic phase	SeHCAT scan, measurement of bile-acid concentrations	Diet low in fat Symptomatic therapy: antidiarrhoeal drugs (loperamide), bile-acid sequestrants (colestyramine)
Carbohydrate malabsorption	50% of pts by the 4 ^o week of pelvic RT 5% in chronic phase	Stool chromatography, oral-tolerance tests that measure blood or breath responses, use of isotope-labelled carbohydrate, direct biopsy proof of enzyme deficiency	Diet low in lactose, fructose, sucrose and starches
Changes in gastrointestinal transit	-	-	Opioids Rotation of antibiotics
Large-bowel strictures	3-15%		Dilatation or stenting, Surgery, Hyperbaric oxygen therapy
Small bowel strictures	9%		
Disease-relapse	4-10%		
New GI tumors	8%		
New-onset inflammatory bowel disease	4%		

Causes and management of symptoms

Causes	Incidence	Diagnosis	Therapy
Loose/semiformed stool			
Small bowel bacterial overgrowth Bile salt malabsorption Carbohydrate malabsorption Changes in transit Development of strictures Neoplasia New onset of primary inflammatory bowel disease	N/A	<u>Laboratory tests:</u> Routine blood screen AND additional blood screen CRP, vitamin B12, thyroid function tests, coeliac screen <u>Breath tests:</u> glucose/lactulose hydrogen breath test for bacterial overgrowth lactose hydrogen breath test <u>Endoscopy:</u>	Antibiotics Off-label treatment: probiotics, prebiotics, promotility agents
Urgency of defecation			
Reduced rectal volume Inflammation Changes in stool consistency Neoplasia		<u>Laboratory tests:</u> routine blood screen including thyroid function tests <u>Endoscopy:</u> flexible sigmoidoscopy <u>Physiology:</u> ano-rectal physiology	Phenylephrine gel
Faecal incontinence			
Mucus-secreting tubulovillous adenoma or carcinoma Inflammatory colitis or proctitis Sphincter defects	40-50%	<u>Endoscopy:</u> flexible sigmoidoscopy <u>Radiology:</u> endoanal ultrasound <u>Physiology:</u> anorectal physiology	Possibly beneficial: Phenylephrine gel (response rate 25%) No data, but possible : Biofeedback Bulking agents, Opiate antagonists Other constipating agents (verapamil) Surgery Toileting exercises Tricyclic antidepressants

Causes and management of symptoms

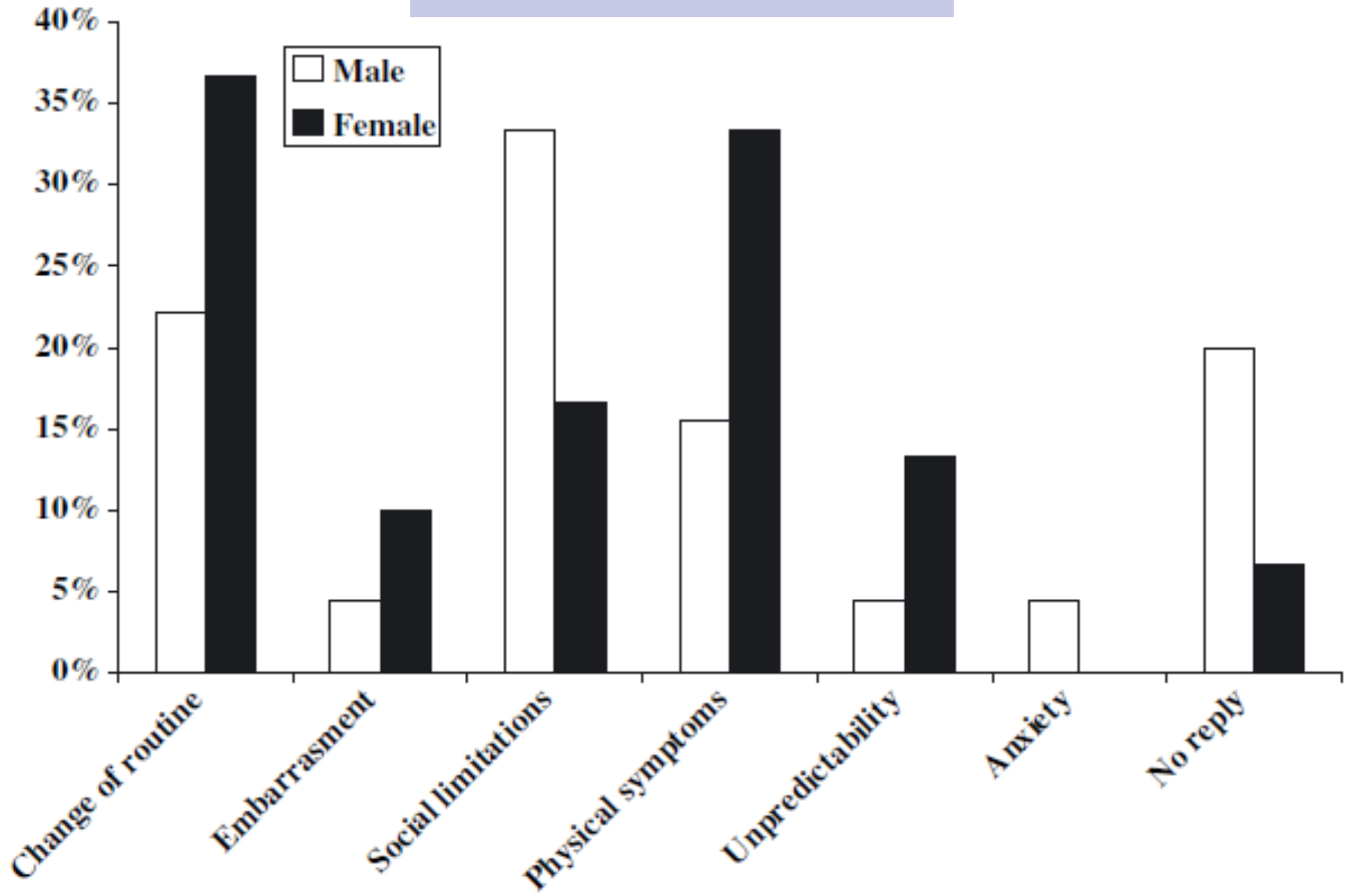
Causes	Incidence	Diagnosis	Therapy
Steatorrhoea			
Pancreatic insufficiency Bile salt malabsorption Small bowel bacterial overgrowth Free fatty acid malabsorption Lymphangectasia	N/A	<u>Laboratory tests:</u> blood screen to exclude Addison's and coeliac disease, thyroid dysfunction vitamin B12 (low in bacterial overgrowth) stool for faecal elastase <u>Breath tests:</u> glucose/lactulose hydrogen breath test for bacterial overgrowth <u>Endoscopy:</u> upper gastrointestinal endoscopy with duodenal aspirate and biopsies <u>Nuclear medicine:</u> SehCAT scan for bile salt malabsorption	Possible beneficial: Bile salt sequestrants Cholylsarcosine Low fat diet Pancreatic enzymes
Anal/rectal pain			
Pelvic or peri-anal sepsi Bowel spasm Faecal loading	30%	<u>Laboratory tests:</u> routine blood screen AND additional blood screen CRP <u>Endoscopy:</u> anoscopy (?fissure) and flexible sigmoidoscopy <u>Radiology:</u> MRI scan pelvis	No data, but possible: Analgesics Antidepressants Gabapentin

Causes and management of symptoms

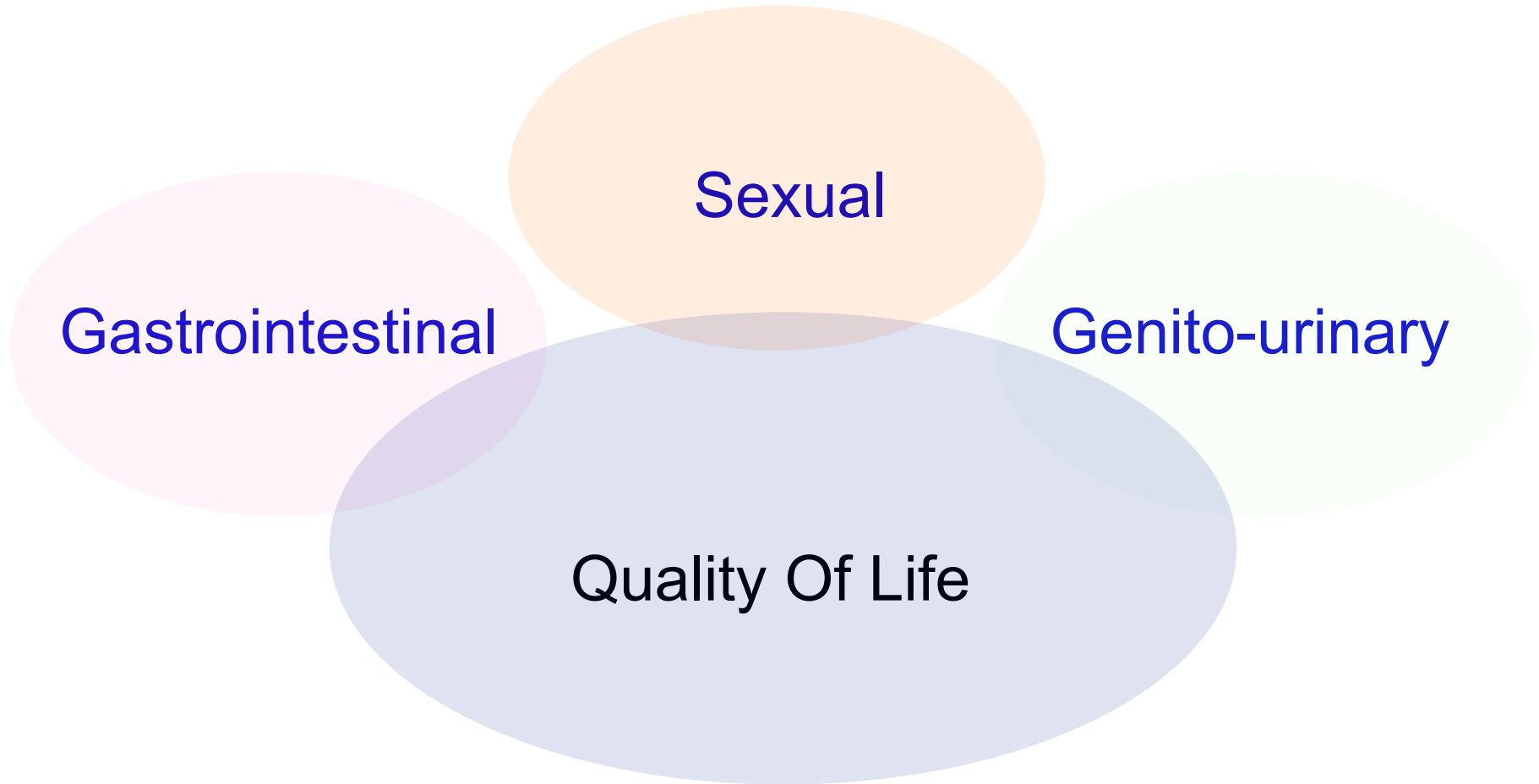
Causes	Incidence	Diagnosis	Therapy
Rectal bleeding			
Teleangectasia, Ulceration	50% of all pts after pelvic RT, but impairs QoL requiring intervention in fewer than 6% The transfusion-dependent bleeding occur in ~5% of all pts	Endoscopy: colonoscopy	Definitely beneficial: Metronidazole, Sucralfate Possible beneficial: Argon beam coagulation Formalin, Heater probe, Hyperbaric oxygen Laser therapy, Pentosan polysulphate Short chain fatty acid enemas, Vitamin A/C/E At best, second line: Corticosteroids, 5-amino salicylic acid (5-ASA), Sulphasalazine
Tenesmus Mucus discharge			
Bacterial overgrowth	25-60%	<u>Endoscopy:</u> flexible sigmoidoscopy check haemoglobin, clotting and haematinics only if heavy bleeding is occurring	<ul style="list-style-type: none"> • Ensure that fibre intake is not excessive • Provide pelvic floor and toileting exercises • Stool bulking agent and/or antidiarrhoeal agent
Excessive flatulence			
Diet too healthy Colonic faecal loading Small intestinal bacterial overgrowth Organic cause (neoplasia, inflammatory bowel disease)	50-60%	<u>Radiology:</u> abdominal X-ray	<ul style="list-style-type: none"> • Dietary: excess/deficiency of fibre intake and inadequate fluid intake • Symptomatic therapy

Bowel Function and Quality of Life

How do they affect quality of life?



Pelvic radiation therapy



Sexual

Gastrointestinal

Genito-urinary

Quality Of Life

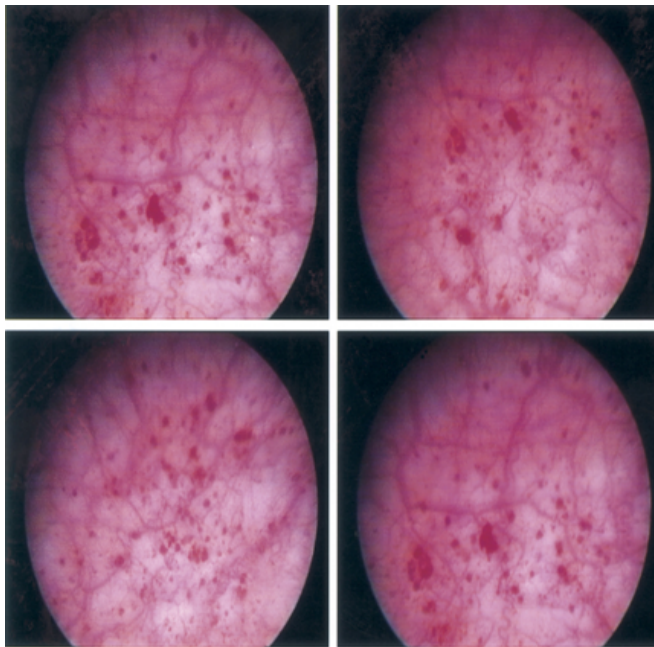
Radiation induced cystitis

- Cystitis describes a clinical syndrome of dysuria, frequency, and occasionally suprapubic pain
- 20% of pts undergo pelvic RT
- Gross haematuria in 3-5% for prostate cancer with RT
- Intractable haematuria in 6.5% of pts with carcinoma of the cervix treated with both intracavitary and external beam RT. Median interval to developing haematuria after RT completing was \sim 35 months.

Radiation induced cystitis

Anatomopathological considerations and Clinical features:

-Acute/subacute phase: within 3-6 months after RT. The histological examination of bladder tissue shows urothelial desquamation, atypia and eosinophilic infiltration. Clinical manifestations are **urinary urgency, pollakiuria and dysuria.**



- Chronic phase: begins 6 months after RT. Late radiation effect on the bladder is ischemia leading to vascular and muscle changes. The vascular endothelial injury causes hyperplasia, occlusion and perivascular fibrosis. The muscle injury cause substitution of smooth muscle fibers with fibroblasts, resulting **decreased bladder capacity and compliance.** Both alterations increase the bladder's susceptibility to mucosal ulceration and **hemorrhage**, with risk of perforation and fistula formation

Radiation induced cystitis

Differential diagnosis:

- Urethral syndrome
- Bladder lesion (calculi, tumor)
- Infection
- Urethritis

Investigation:

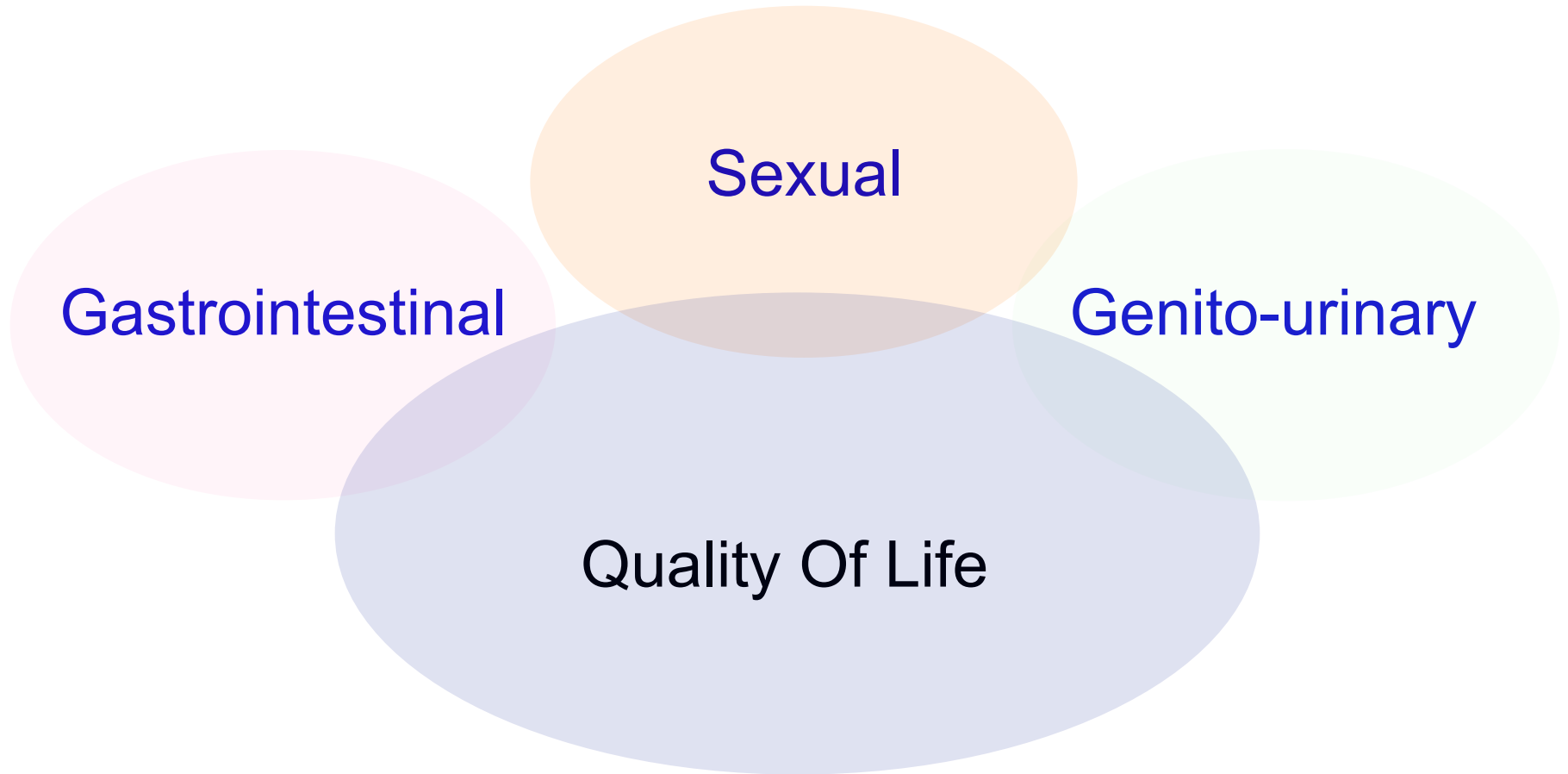
- Urine dipstick
- Urethrocystectomy and/or urine cytology

Radiation induced cystitis

Treatments options:

- **Prevention:** uroprotective agents (mesna, amifostine)
- **Acute phase:**
 - FANS and/or
 - Antibiotics
 - Blueberry integrators
- **Chronic phase:**
 - Intravesical treatment (Intravesical hyaluronic acid, Intravesical aluminum, bladder formalin instillation)
 - Systemic treatment (Pentosan polysulfate, Oral aminocaproic acid)
 - Physical procedures (Hyperbaric chamber, embolization, cystectomy)

Pelvic radiation therapy



Sexual

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Quality Of Life

Sexual problems

- 40-100% of cancer patients experience some form of sexual dysfunction
- Issues do not always resolve after therapy
- Almost all cancer treatments have the potential to alter sexual function (surgery, chemotherapy, radiation, hormones)
- Represents major quality of life (QOL) issue
- With intervention, up to 70% of patients can have improved functioning

Male sexual dysfunction

- Erectile dysfunction (ED)
 - Neurogenic
 - Vascular
 - Psychologic
 - Painful erection
 - Priapism
- Orgasmic disorders
 - Delayed or absent orgasm
 - Premature ejaculation
 - Retrograd ejaculation
- Sexual pain disorders
- Sexual desire disorders

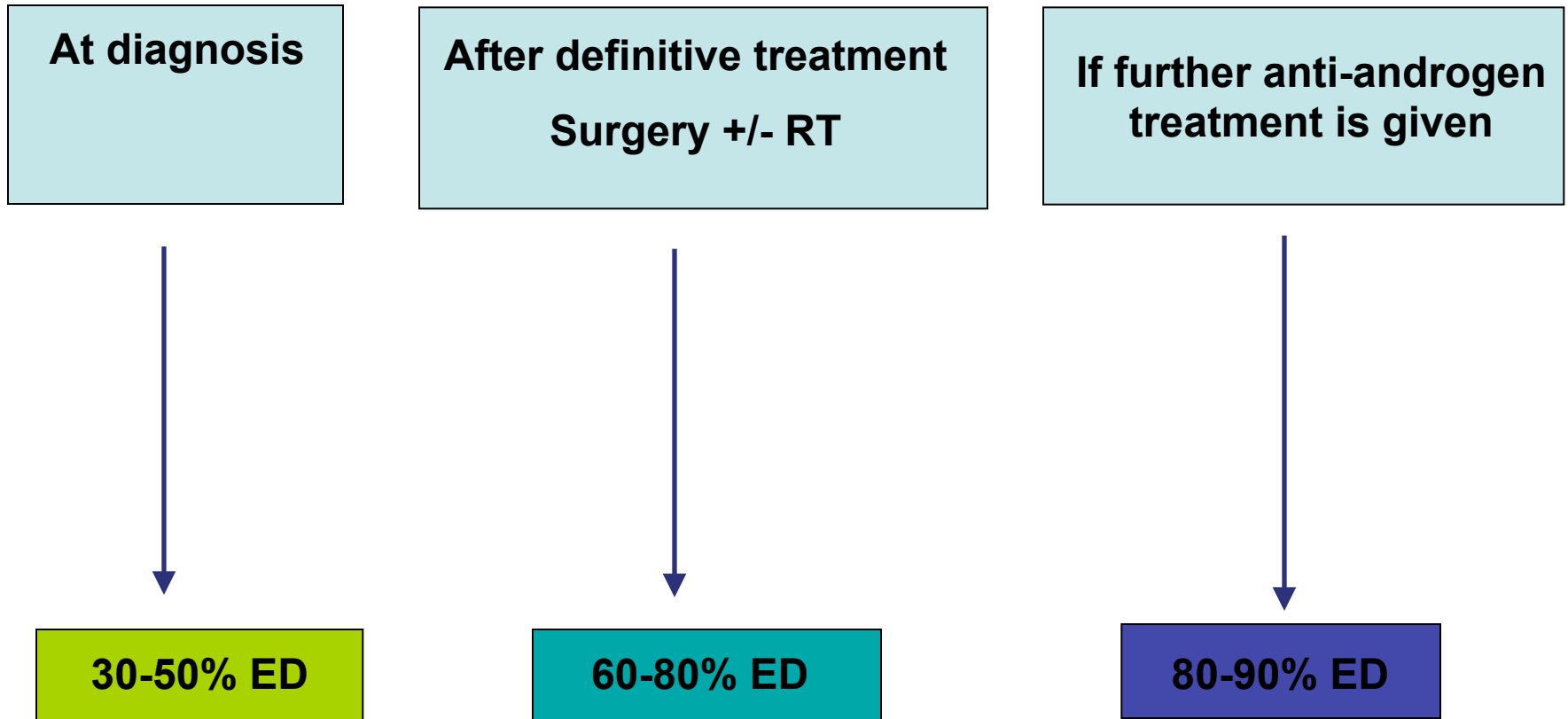
Prostate cancer and erectile dysfunction

Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: A critical review

Systematic review

2007

Gerard J. van der Wielen^{a,*}, John P. Mulhall^b, Luca Incrocci^a

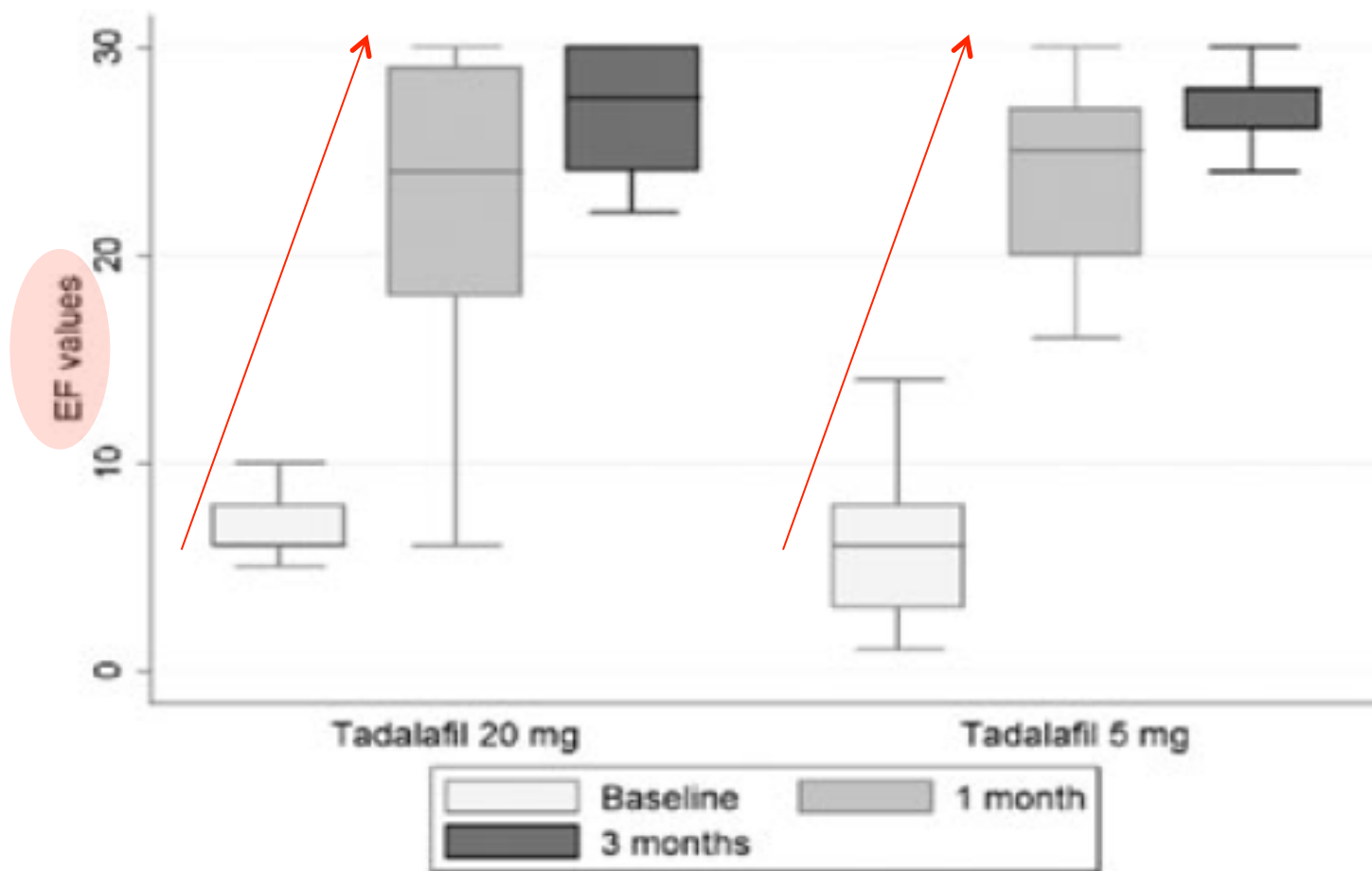


Interventions for Male Issues

- Communication (therapy) with the patient and the partner
- Pharmacological
 - Hormone replacement therapy (locally and/or systemically)
 - Phosphodiesterase inhibitors (e.g. Viagra)
 - Tibolone
 - Testosterone
 - Prostaglandine locally
- Aids
 - Penile transplants

Efficacy and Safety of Tadalafil 20 mg on Demand vs. Tadalafil 5 mg Once-a-Day in the Treatment of Post-Radiotherapy Erectile Dysfunction in Prostate Cancer Men: A Randomized Phase II Trial

Umberto Ricardi, MD,* Paolo Gontero, MD,† Patrizia Ciammella, MD,* Serena Badellino, MD,* Franco Valentino, MD,† Fernando Munoz, MD,* Alessia Guarneri, MD,* Nadia Rondi, MD,* Francesco Moretto, MD,* Andrea Riccardo Filippi, MD,* Riccardo Ragona, MD,* and Alessandro Tizzani, MD†



RTOG 0831

A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED PHASE III TRIAL TO EVALUATE THE EFFECTIVENESS OF A PHOSPHODIESTERASE 5 INHIBITOR, TADALAFIL, IN PREVENTION OF ERECTILE DYSFUNCTION IN PATIENTS TREATED WITH RADIOTHERAPY FOR PROSTATE CANCER

- Clinical stage T1b-T2b (AJCC, 6th ed.)

S T R A T I F I F Y	<u>Age</u>	R A N D O M I Z E	<u>Arm 1</u>
	1. ≤65 years 2. >65 years		Tadalafil started within 7 days after the start of radiation therapy* and continued for 168 days (24 weeks)
	<u>RT Treatment</u>		<u>Arm 2</u>
	1. External radiation therapy 2. Brachytherapy*		Placebo started within 7 days after the start of radiation therapy* and continued for 168 days (24 weeks)

- Target accrual: 218 /// Current Accrual: 175
- Primary endpoint: determine whether tadalafil maintains spontaneous (off-drug) erectile function at 28-30 weeks after RT initiation

Female Sexual dysfunction

- Sexual desire disorders / reduced sexual interest
- Sexual arousal disorders
 - Reduced/inhibited vaginal lubrication
 - Reduced subjective feeling of being aroused
- Orgasmic disorders
 - Premature, delayed or absent orgasm following a normal excitement phase
- Sexual pain disorders
 - Dyspareunia
 - Vaginismus

Interventions for Female Issues

- Vaginal lubricants

- Use before/during sexual activity
- Water soluble, water- or silicone-based
- Petroleum-based can damage condoms and encourage vaginal infection

- Vaginal Moisturizer

- Replens: 3x a week, for a minimum of 3 months
- Vaginal tissue regains moisture & elasticity
- Use with lubricants, can also use Replens before intercourse

- Vaginal Estrogens

- Creams: use 2-3x week
- Causes elevated systemic estrogen (highest in first 3-4 mos), not good for breast cancer pts
- E-string: silicone ring, slow release of local estrogen over three months

Risk of Infertility with Radiation Therapy

- Small dose can = big damage
- Temporary or permanent
- >40 yrs old: 5-6 Gy; <40 yrs old: 20 Gy for permanent ovarian failure
- Spontaneous abortion: 38% vs. 12% (in the general public)
- Preterm labor: 62% vs. 9%
- Low birth weight: 62% vs. 6%

Table 2. Risks of Permanent Amenorrhea in Women Treated With Modern Chemotherapy and Radiotherapy

Degree of Risk	Cancer Treatment
High risk (> 80%)	Hematopoietic stem cell transplantation with cyclophosphamide/total body irradiation or cyclophosphamide/busulfan
	External beam radiation to a field that includes the ovaries
	CMF, CEF, CAF × 6 cycles in women age 40 and older (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)
Intermediate risk	CMF, CEF, CAF × 6 cycles in women age 30-39 (adjuvant breast cancer therapy with combinations of cyclophosphamide, methotrexate, fluorouracil, doxorubicin, epirubicin)
	AC × 4 in women age 40 and older (adjuvant breast cancer therapy with doxorubicin/cyclophosphamide)

Options for Fertility Preservation in Women

- **Embryo freezing** : cycle 12-14 days, 10-25% chance of pregnancy per embryo stored, cost \$8-12,000, then cost of storage, thaw & implanting
- **Ovarian transposition** : move ovaries from XRT field, can be laparoscopic, cost ?, 16-90% success rate
- **Egg cryopreservation** : cycle 12-14 days, 2% chance of live birth per thawed egg

Options for fertility preservation in men

- **Sperm banking** – only after puberty
 - Although many men have poor quality sperm at diagnosis, new techniques can use it anyway (even just 1-2 samples)
 - No sex for 5 days prior, 24-48 hours between samples; Testicular aspirate if no semen
- **Intracytoplasmic sperm injection (ICSI)**
 - Newer technique for fertilization, very successful
- **GnRH agonist/antagonists**
 - “Turn off” gonads (only tested in mice, no births)
- **Cryopreservation** of testicular tissue, then transplant or grow in vivo (+ births in mice)

Conventional Techniques to Reduce Pelvic Radiation Toxicity

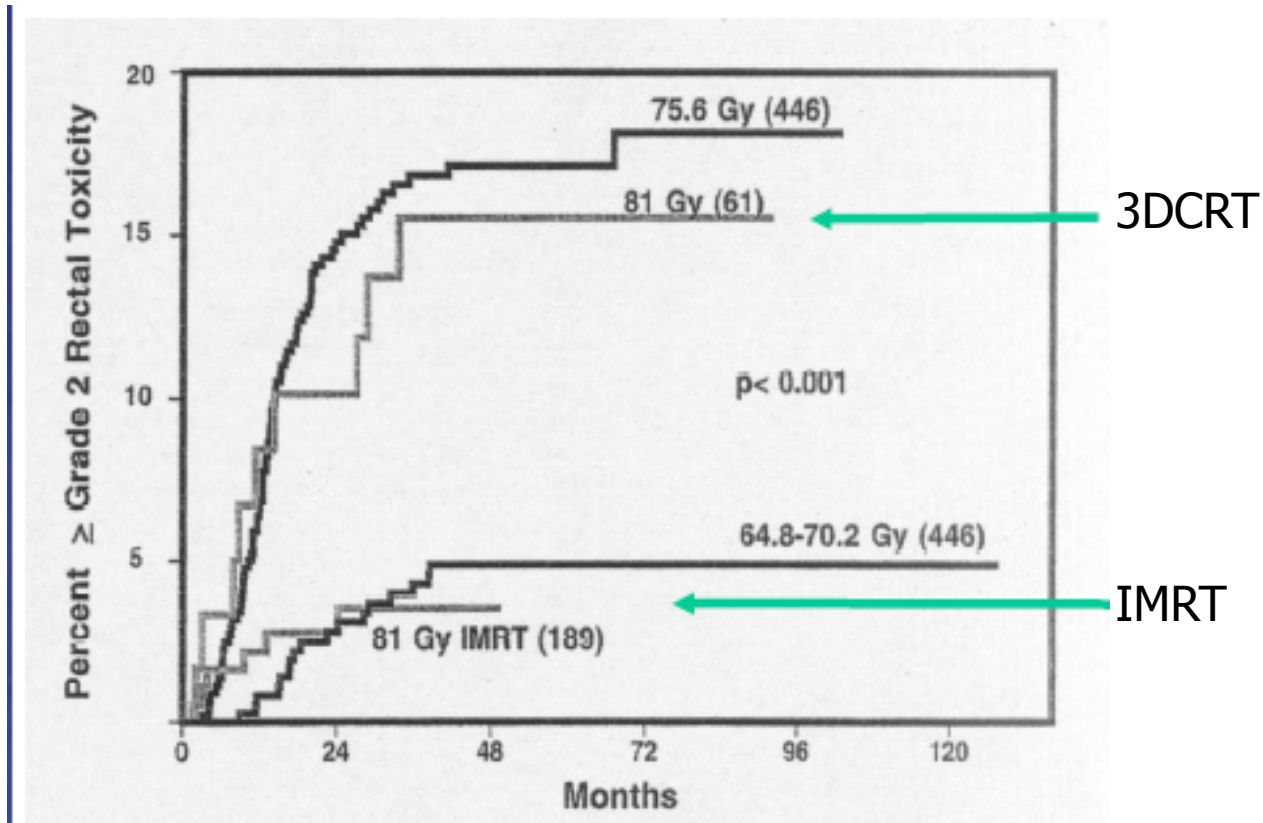
Complications of pelvic radiotherapy are a function of the volume of the radiation field, overall treatment time, fraction size, radiation energy, total dose, and technique.

- 3D-CRT with three-field technique versus "box" technique
- Prone position (with belly boards)
- Full bladder
- High-energy photons

Potential interventions to minimise the development of RT toxicity

Impact of new technology

IMRT Significantly Reduces Rectal Complications





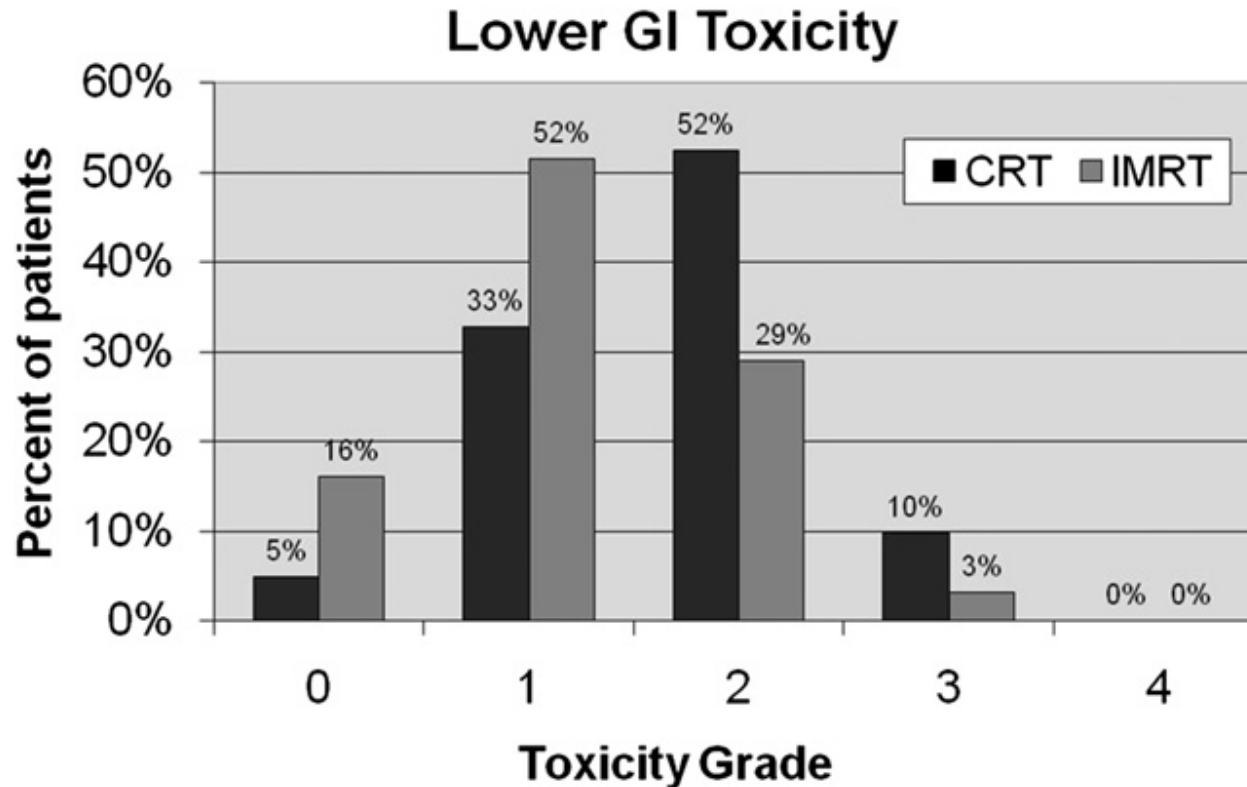
doi:10.1016/j.ijrobp.2011.01.051

CLINICAL INVESTIGATION

REDUCED ACUTE BOWEL TOXICITY IN PATIENTS TREATED WITH INTENSITY-MODULATED RADIOTHERAPY FOR RECTAL CANCER

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Take home messages:

National Cancer
Survivorship Initiative
Vision

British Journal of Cancer (2011)

Editorial

The National Cancer Survivorship Initiative: new and emerging evidence on the ongoing needs of cancer survivors

Key needs:

- 1) a personalized “survivorship” care plan formulated for each patient on completion treatment
- 2) support to self-manage their condition if appropriate
- 3) provision of information on long-term effects of living with and beyond cancer
- 4) access to specialist medical care for complications that occur after cancer