Incontri Bresciani di Radioterapia Oncologica – Edizione 2014
Brescia Meetings in Radiation Oncology – 2014 Edition

NORTHWEST PASSAGE: KEY-FUNCTIONS PRESERVATION IN ONCOLOGY

Brescia – September 25th/26th, 2014

Surgery/radiotherapy/chemotherapy interactions and treatment damage: the case of gynaecologic cancer

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NORTHWEST PASSAGE: KEY-FUNCTIONS PRESERVATION IN ONCOLOGY

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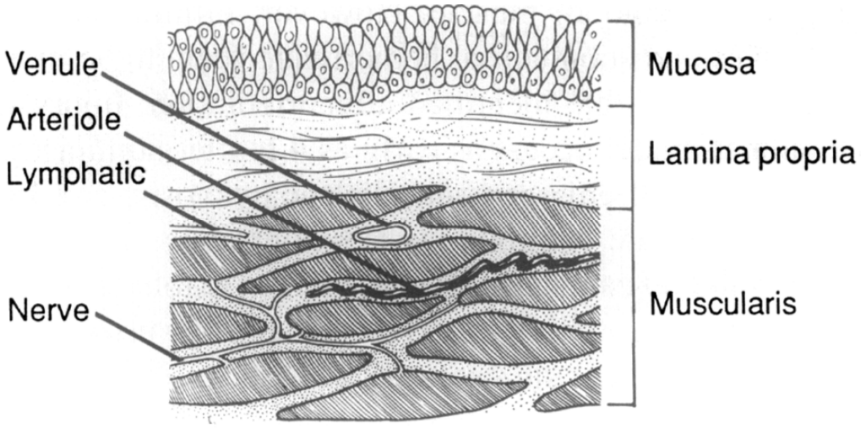
The study of normal tissue side effects has 3 main aims:

1 - to serve as an integral part of quality assurance in routine practice, including ongoing management of morbidity;

2 - to establish the type, incidence and severity of effects for specific therapies to inform the decision making by patients, physicians, and health care managers;

3 - to investigate the pathobiology underlying these effects, and thereby develop strategies for their prevention or amelioration

BLADDER INJURY

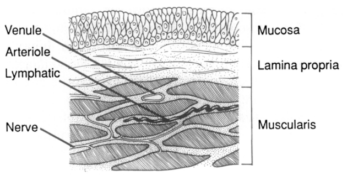


The ***smooth muscle*** of the urinary bladder is sensitive to irradiation.

Oedema occurs early and may be followed by cellular destruction.

Normal smooth muscle may be replaced by fibroblasts and ultimately increased collagen deposition leading to decreased bladder compliance and both functional and anatomical changes in bladder capacity.

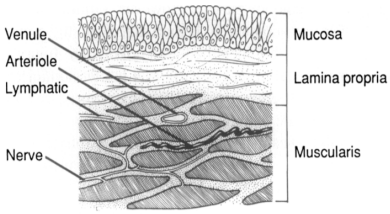
BLADDER INJURY



3 months following irradiation, intermediate and basal urothelial cells show signs of damage including nuclear irregularity, cellular edema, and increased cytoplasmic elements

Signs of endothelial cell damage and perivascular fibrosis occurs by 6 to 12 months. Vascular occlusion and focal bladder ischemia may result.

Available information supports the concept that late bladder fibrosis is secondary to vascular ischemia of the bladder wall.



Damage to the bladder or urethra may result:

Reduced capacity to store or expel urine
Episodic or, more rarely, ***continuous urinary incontinence.***

As both exteroceptive and proprioceptive nerve endings exist in the bladder, damage to the bladder may result in:

Considerable ***pain***
Frequent ***contractions*** of the organ and ***incontinence***.

Urological complications after treatment of cervical cancer

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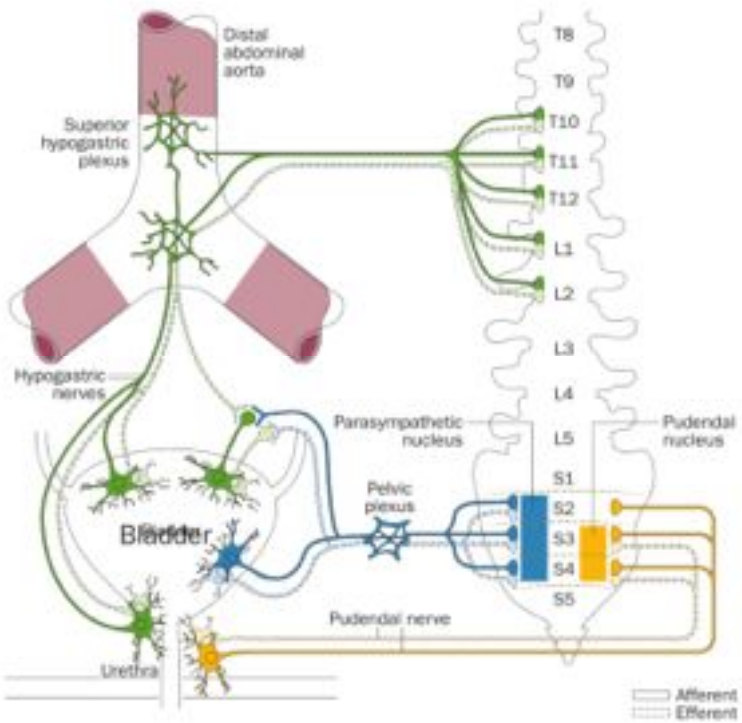
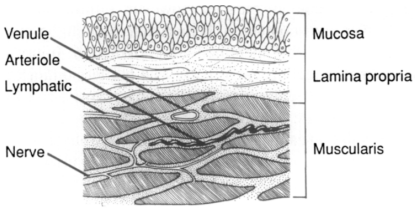


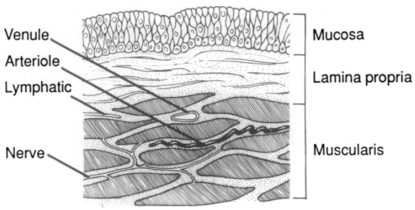


Chemotherapeutic agents may affect bladder function through excretion of active metabolites in the urine or by increasing the damaging effects of irradiation when used concurrently with this form of therapy.

Normally, chemotherapy has little effect on bladder function considerable toxicity has been observed with the use of ***Cyclophosphamide***, ***Ifosfamide*** may also cause bladder damage.

Irritative voiding symptoms, hemorrhagic cystitis, and bladder contracture. Hemorrhagic cystitis may occur at any time after administration and may be transient and mild or persistent and major.

The toxicity of cyclophosphamide is caused by ***acrolein***, a liver metabolite.



In a mouse model, cyclophosphamide toxicity occurred early, within 1 week of administration, compared to toxicity of radiation which occurred late.

When cyclophosphamide was administered before or after irradiation, an early, dose-related effect of irradiation was noted.

Urothelial toxicity may be reduced by a variety of methods
- increased hydration
- frequent voiding
- catheter drainage
- constant bladder irrigation
- and reduced doses of drug

all designed to limit the concentration of acrolein within the urinary bladder

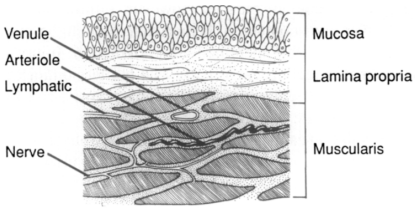


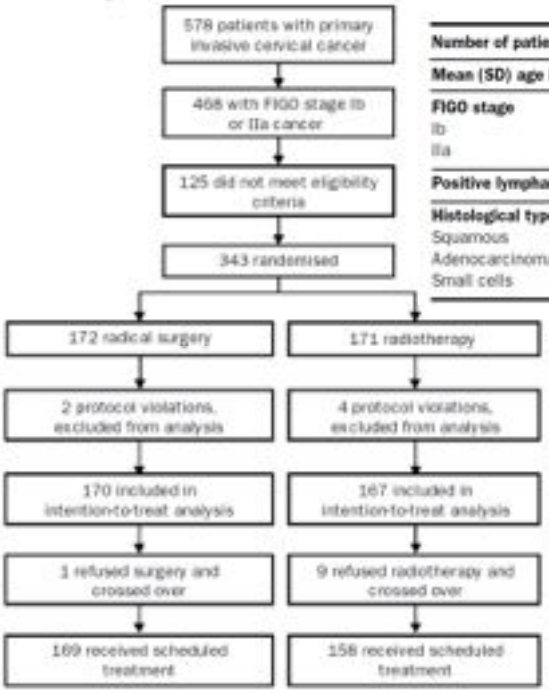
Table 10. Bladder complication summary*

Disease treated	Approximate dose to ≥ 50% of the bladder (Gy)	Approximate maximum bladder dose (Gy)	Approximate clinical complication rate (%)
Prostate	40	60–65	5
Bladder	50–65	50–65	5–20†
Cervix	40	65–75	5–10
	40	≥ 80	10–20
Rectal	40–50	40–50	0

Int. J. Radiation Oncology Biol. Phys., Vol. 31, No. 5, pp. 1257–1280, 1995

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

Fabio Landoni



	Surgery (n=170)		Radiotherapy (n=167)	
	≤4 cm	>4 cm	≤4 cm	>4 cm
Number of patients	115	55	113	54
Mean (SD) age in years	51·8 (11·3)	46·1 (10·1)	55·2 (10·9)	50·0 (9·8)
FIGO stage				
Ib	107 (93%)	47 (85%)	99 (88%)	45 (83%)
IIa	8 (7%)	8 (15%)	14 (12%)	9 (17%)
Positive lymphangiography	12 (10%)	12 (22%)	9 (8%)	13 (24%)
Histological type				
Squamous	94 (82%)	44 (80%)	97 (86%)	45 (83%)
Adenocarcinoma	18 (16%)	8 (15%)	13 (11%)	7 (13%)
Small cells	3 (2%)	3 (5%)	3 (3%)	2 (4%)

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

Fabio Landoni

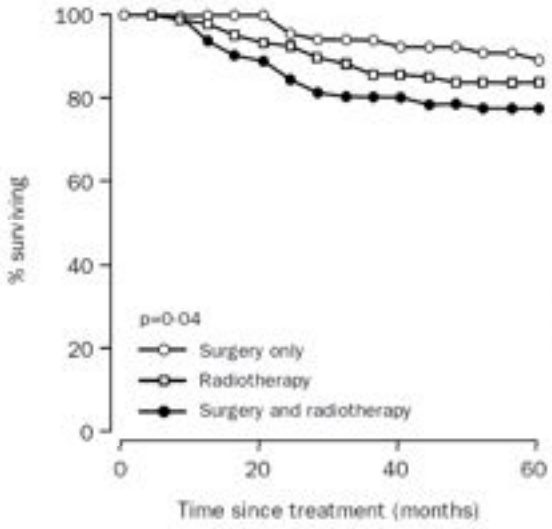


Figure 4: **Overall actuarial survival by treatment group**

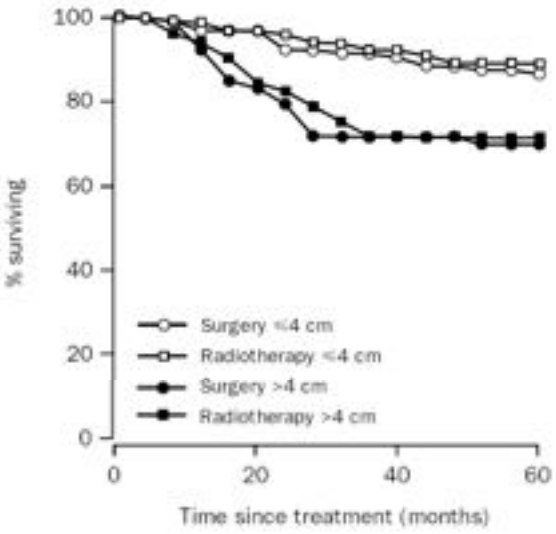


Figure 3: **Overall actuarial survival by treatment group and cervical diameter**

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

Fabio Landoni

Classification of complications

grade 1, mild symptoms not affecting the patient's health and easily cured;

grade 2, symptoms that can be resolved by long-term medical therapies;

grade 3, major symptoms that require surgery or invasive procedures and affect the performance status of the patient, or fatal complications.

11 patients died of

- intercurrent disease
- two from fatal complications (bowel perforation and pulmonary embolism)

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

Fabio Landoni

	Surgery						Radiotherapy group	
	Surgery only		Surgery plus radiotherapy		Total			
	≤4 cm	>4 cm	≤4 cm	>4 cm	≤4 cm	>4 cm	≤4 cm	>4 cm
Number of patients	53 (52)	9 (9)	62 (62)	46 (46)	115 (114)	55 (55)	113 (105)	54 (53)
Relapses	7 (13%)	2 (22%)	15 (26%)	17 (37%)	23 (20%)	19 (34%)	21 (18%)	23 (42%)
Pelvic	4	2	7	9	11	11	12	16
Distant	3	. .	9	8	12	8	9	7
Morbidity								
Grade 2–3†	16 (31%)	3 (33%)	18 (29%)	11 (24%)	34 (30%)	14 (25%)	13 (12%)	6 (11%)
Short-term	10 (16%)		22 (20%)		32 (19%)		11 (7%)	
Long-term	15 (24%)		31 (29%)		46 (27%)		25 (16%)	

(p=0·0004)

†Parentheses show number of patients who actually received this treatment instead of intention to treat. ‡% calculated for number of patients who actually received treatment.

Table 3: **Relapses and morbidity**

THE LANCET Vol 350 • August 23, 1997

Urological complications after treatment of cervical cancer

www.nature.com/nrurol
FEBRUARY 2014

Key points

- The exact incidence of lower urinary tract dysfunction after treatment of cervical cancer is not known, but it has decreased in the past two decades
- Frequently occurring urological disorders after radical surgery are hypocontractility of the bladder, detrusor overactivity, incontinence and low-compliance bladder
- Neuroanatomical knowledge and concomitant nerve-sparing surgery are essential to reduce lower urinary tract dysfunction after radical hysterectomy
- Radiation-induced urological complications include radiation cystitis, ureteric stenosis, fibrotic, shrunken, low-compliance bladder and fistula formation
- Owing to the development of image-guided radiotherapy, fewer radiation-induced urological complications have been reported since 1990

Urological complications after treatment of cervical cancer

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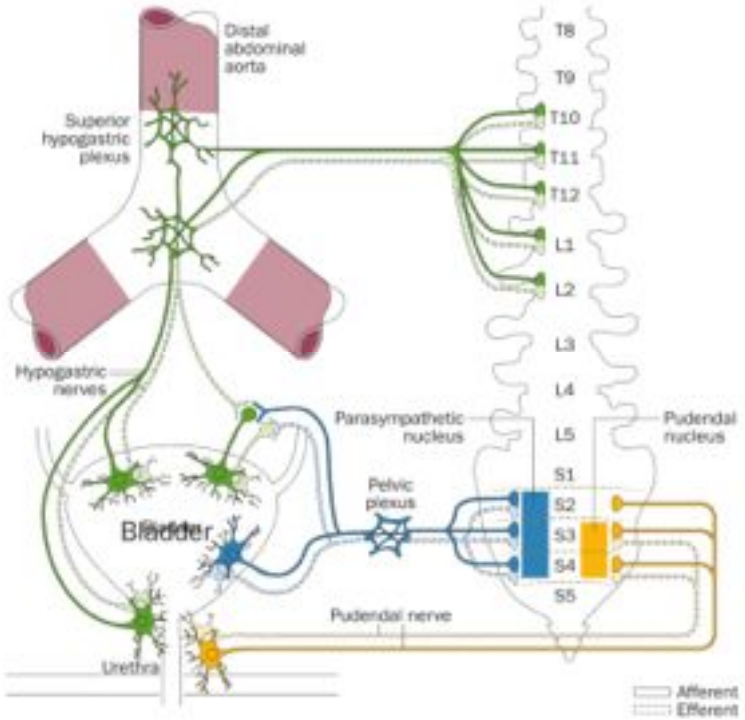

Urological complications after treatment of cervical cancer

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Radical hysterectomy: **Classification**

Class I hysterectomy	Modified hysterectomy with limited excision of the paraametrial tissue. Mainly used for in situ carcinoma
Class II hysterectomy	Removed the median half of the cardinal and sacrouterine ligaments and the uetrine vessels are ligated just medial to the ureters
Class III hysterectomy	So called Wertheim-Meigs: wider dissection of the parametrium, ligation of the uterine artery at its origin from its origin from the internal iliac artery, excision of the sacrouterine ligament at the sacral attachment, complete removal of cardinal ligament at the pelvic wall, resection of half of the vagina
Class IV hysterectomy	Dissection of the ureter from the pubovescical ligament, ligation of superior vescical artery and excision of ¾ of vagina
Class V hysterectomy	Excision of the affected portion of the distal ureter or bladder

Urological complications after treatment of cervical cancer

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Long term urological compications after radical hysterectomy

Class II nerve-sparing	5%
Class II + postop RT	20%
Class III non-nerve sparing	30%
Class III + postop RT	37%

Urological complications after treatment of cervical cancer

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Common complications after **radical hysterectomy** with complete excision of the parametrium:

Lower Urinary Tract Dysfunction (LUTD)	70 – 80%
problems with bladder storage and evacuation	70 – 80%
+/- dysuria	
hypocontractility of the bladder	
detrusor overactivity	21%
incontinence	30 - 50%
low compliance bladder	
Less frequent disorders:	
hydronephrosis	10 – 20%
fistula	0,9 – 2,7%
intraoperative injuries of the bladder	0,4 – 3,7%

Urological complications after treatment of cervical cancer

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Common complications after

Radiation and Chemotherapy

Haemorrhagic cystitis

5,8%	in 5 years
7,4%	in 10 years
9,6%	in 20 years

Ureteric stenosis (exluded the recurrent disease)

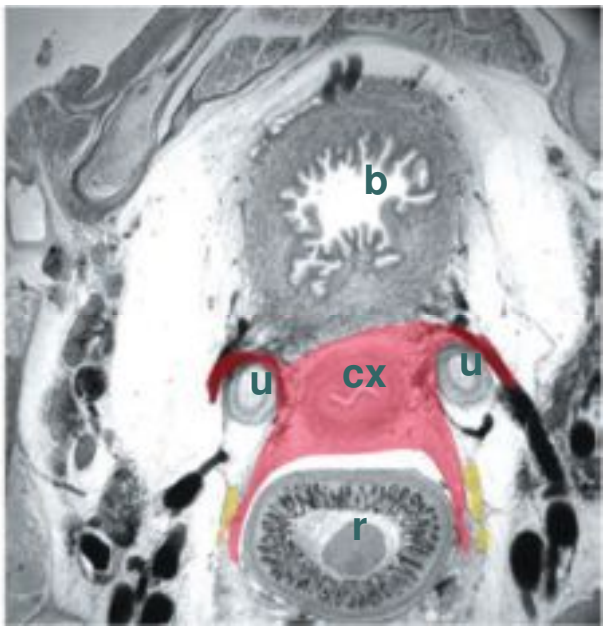
1,0%	at 5 years
1,2%	at 10 years
2,2%	at 15 years
2,5%	at 25 years

Low-compliance Bladder

Similar to the radical hysterctomy group of patients

Fistula 50% of Stage IV patients

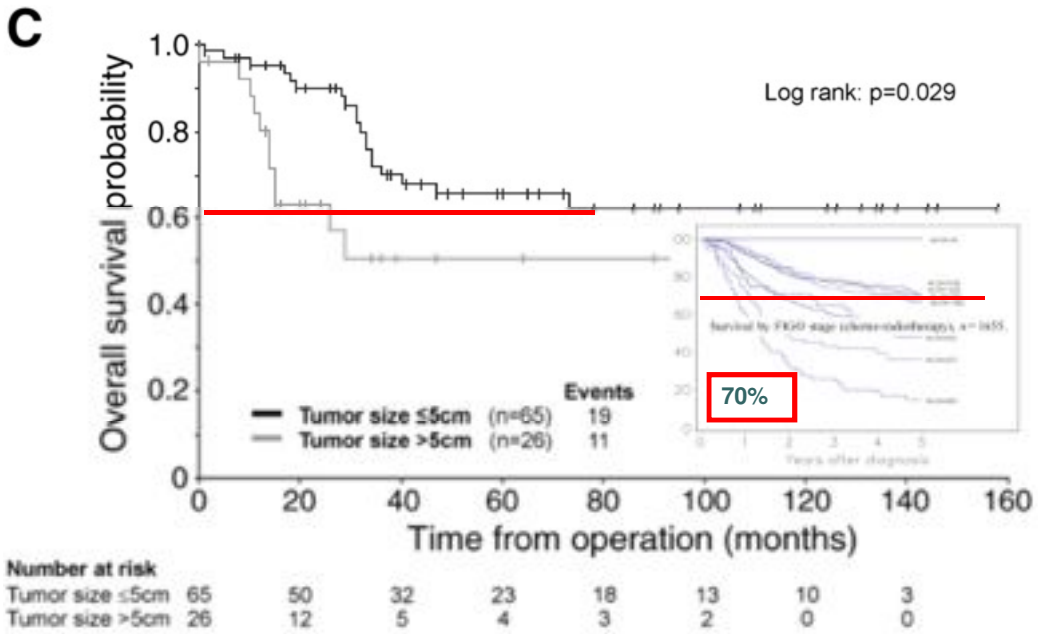
Association between the mesenchymal compartment of uterovaginal organogenesis and local tumour spread in stage IB–IIB cervical carcinoma: a prospective study Michael Hokel, Leipzig.



Transverse sections of a female fetus aged 24 weeks at the level of ureters (u) entering bladder (b), and of a female fetus aged 17 weeks at the level where ureters are lateral to the cervix (cx).

Lancet Oncol 2005; 6: 751–56

(Laterally) Extended Endopelvic Resection: Surgical treatment of locally advanced and recurrent cancer of the uterine cervix and vagina based on ontogenetic anatomy



Gynecologic Oncology 127 (2012) 297–302

(Laterally) Extended Endopelvic Resection: Surgical treatment of locally advanced and recurrent cancer of the uterine cervix and vagina based on ontogenetic anatomy

Types of (Laterally) Extended Endopelvic Resection and reconstructive procedures.

(L)EER type (n = 91)	25	Abdominal, anterior
	28	Abdominal, total
	15	Abdominoperineal, anterior
	1	Abdominoperineal, posterior
	21	Abdominoperineal, total
	1	Perineal, posterior
LEER type (n = 83)	66	Caudal
	2	Rostral
	15	Caudal and rostral
Reconstruction of urethrovesical function	44	Colon conduit
	19	Ileum conduit
	19	Colon pouch
	5	Ileum neobladder
Reconstruction of anorectal function	46	Colostomy
	4	Colorectal anastomoses
	2	Rectal J pouch
Reconstruction of vaginal function	6	Sigma neovagina
	4	Pudendal thigh neovagina
	3	Gluteal thigh neovagina
	1	Rectus abdominis neovagina
Pelvic lymph node dissection	52	
Paraaortic lymph node dissection	72	

Gynecologic Oncology 127 (2012) 297–302

(Laterally) Extended Endopelvic Resection: Surgical treatment of locally advanced and recurrent cancer of the uterine cervix and vagina based on ontogenetic anatomy

Moderate and severe complications.

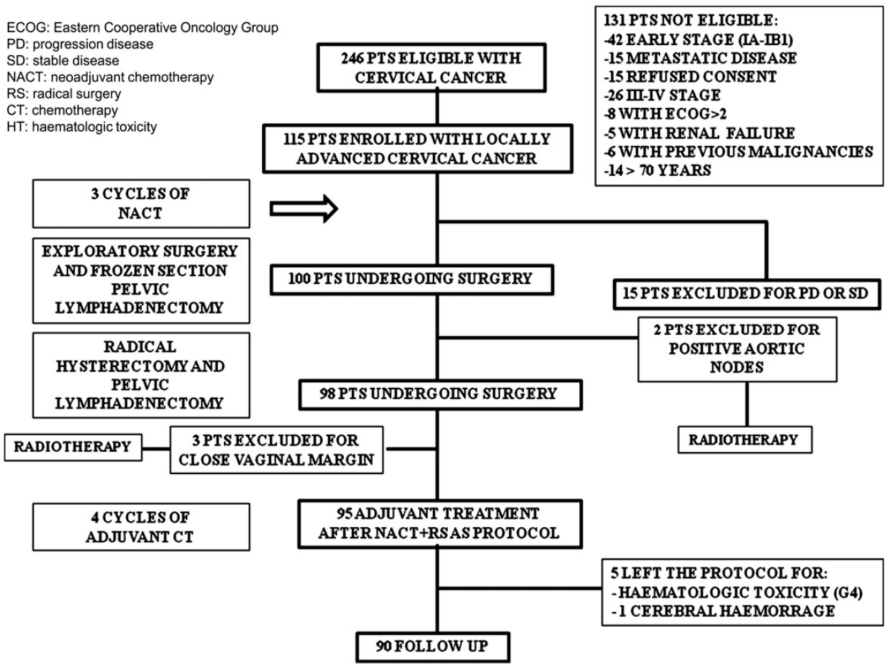
Complication	Early			Late		
	G2	G3	G4	G2	G3	G4
Cardiopulmonary[1]	2					
Cutaneous[2]	8			3		
Gastrointestinal[3]	6	3		4		
Neurologic[4]	2					
Urinary[5]	6	1	1	1	1	
Vascular[6]	8	4		3		

32 11

[1] Pneumonia, pulmonary edema.
[2] Laparotomy dehiscence, partial flap necrosis, donor site dehiscence, perineal hernia.
[3] Bowel obstruction, anastomosis insufficiency, bowel fistula, generalized peritonitis, rectum stump dehiscence, pelvic abscess, parastomal hernia.
[4] Temporary paresis of femoral and sciatic nerve.
[5] Anastomotic insufficiency, ischemic necrosis of conduit, pouch neobladder; stenosis of urostoma, pouch incontinence, hydronephrosis.
[6] Postoperative bleeding, deep venous thrombosis, pulmonary embolia, infected lymphcyst, leg edema.

Gynecologic Oncology 127 (2012) 297–302

Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer



Gynecologic Oncology 127 (2012) 290–296

Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer

Side effects of chemotherapy.[a]

Neoadjuvant chemotherapy					
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Total %
Hematologic	15	20	6	2	37
Nausea/vomiting	21	32	2	2	50
Cardiovascular	0	0	0	0	0
Skin	4	2	0	0	5
Neuropathy	10	14	0	0	21
Allergy	0	9	3	0	10
Hemorrhage	0	0	0	0	0
Hepatic	3	2	1	0	5
Alopecia	67	28	/	/	95

[a] The same patient may have more than a side effect.

Gynecologic Oncology 127 (2012) 290–296

Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer

Complications data			(%)	G Dindo clas.
Intraoperative injuries	Urinary tract	Ureteral Bladder	3 (3%)	Grade III
	Bowel		2 (2%)	Grade III
	Vessels		6 (6%)	Grade III
Postoperative	Fever		15 (15%)	Grade II
	Urinary infection		4 (4%)	Grade II
	Wound infection		7 (7%)	Grade II
	Wound dehiscence		2 (2%)	Grade II
	Bowel occlusion		4 (4%)	Grade II
	Fistula		2 (2%)	Grade III
	Symptomatic lymphocysts		14 (14%)	Grade II Grade I
	Pelvic abscess		5 (5%)	Grade II Grade III

Dindo D, Dematrtines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and result of a survey. Ann Surg 2004;240:205-13.

Gynecologic Oncology 127 (2012) 290–296

Classification of Surgical Complications

A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

Dindo D, Dematrtines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and result of a survey. Ann Surg 2004;240:205-13.

CISPLATIN, RADIATION, AND ADJUVANT HYSTERECTOMY COMPARED WITH RADIATION AND ADJUVANT HYSTERECTOMY FOR BULKY STAGE IB CERVICAL CARCINOMA

HENRY M. KEYS, M.D., BRIAN N. BUNDY, PH.D., FREDERICK B. STEHMAN, M.D., LAILA I. MUDERSPACH, M.D., WELDON E. CHAFE, M.D., CHARLES L. SUGGS III, M.D., JOAN L. WALKER, M.D., AND DEBORAH GERSELL, M.D.

TABLE 3. ADVERSE EFFECTS.*

ADVERSE EFFECT	RADIOTHERAPY ALONE (N=186)					RADIOTHERAPY AND CISPLATIN (N=183)				
	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	number of patients									
Hematologic	149	18	16	3	0	42	36	66	33	6
Gastrointestinal	114	36	27	4	5	51	57	49	17	9
Genitourinary	145	24	11	5	1	123	43	14	1	2
Cutaneous	165	10	7	3	1	158	18	7	0	0
Neurologic	184	0	1	1	0	167	6	8	2	0
Other	163	7	11	4	1	137	24	10	9	3

PELVIC RADIATION WITH CONCURRENT CHEMOTHERAPY COMPARED WITH PELVIC AND PARA-AORTIC RADIATION FOR HIGH-RISK CERVICAL CANCER

MITCHELL MORRIS, M.D., PATRICIA J. EIFEL, M.D., JIANDONG LU, PH.D., PERRY W. GRIGSBY, M.D., CHARLES LEVENBACK, M.D., RANDY E. STEVENS, M.D., MARVIN ROTMAN, M.D., DAVID M. GERSHENSON, M.D., AND DAVID G. MUTCH, M.D.

TABLE 4. WORST SIDE EFFECTS OF TREATMENT OCCURRING OR PERSISTING MORE THAN 60 DAYS AFTER THE COMPLETION OF TREATMENT.*

SITE OF SIDE EFFECT	RADIOTHERAPY AND CHEMOTHERAPY (N=193)†		RADIOTHERAPY ALONE (N=193)	
	GRADE 3	GRADE 4	GRADE 3	GRADE 4
	number of patients (percent)			
Skin or subcutaneous tissue	1	0	0	1
Small bowel	1	4	0	7
Large bowel or rectum	4	13	2	17
Bladder	4	1	1	2
Ureters	1	2	0	2
Other	2	1	1	3
Maximal grade of toxicity	8 (4)	16 (8)	2 (1)	20 (10)

*A grade of 3 indicates a moderate effect, and a grade of 4 a severe effect.

†No follow-up data were available for two patients.

Efficacy bevacizumab added to CRT for cervical carcinoma

RTOG 0417

Table 2 Protocol-defined treatment-related adverse events occurring at any time (n=49)

Category	Grade 3	Grade 4
Blood/bone marrow	11	3
Cardiovascular (general)	1	0
Gastrointestinal	3	0
Neurology	1	1
Renal/genitourinary	1	1
Worst nonhematologic	4 (8.2%)	2 (4.1%)
Worst overall	13 (26.5%)	5 (10.2%)

International Journal of Radiation Oncology • Biology • Physics

THE RESPONSE OF THE URINARY BLADDER, URETHRA, AND URETER TO RADIATION AND CHEMOTHERAPY

Int. J. Radiation Oncology Biol. Phys., Vol. 31, No. 5, pp. 1257–1280, 1995

Table 5. Frequency (%) of urinary sequelae following XRT for cervical cancer

Total bladder dose (Gy)	Montana *et al.* (91)*	Pourquier *et al.* (108)*	Perez et al. (101, 102)‡
≤ 60.00	2.9 (6/204)	3.0 (5/164)	2.0 (4/199)
60.01–65.00	7.0 (7/100)	9.1 (9/98)	4.7 (10/214)
65.01–70.00	5.0 (5/100)	13.0 (14/108)	
70.01–75.00	7.5 (4/53)	7.2 (6/83)	4.3 (10/235)
75.01–80.00	9.1 (3/33)	23.4 (15/64)	
≥ 80.00	10.8 (4/37)	28.0 (30/107)	11.1 (18/162)

* All urinary complications; ‡Moderate or severe complications only. The numbers of patients are shown in parentheses.

Uptake and outcomes of intensity-modulated radiation therapy for uterine cancer

"…the use of IMRT has increased over time for women with uterine cancer undergoing pelvic radiotherapy…"

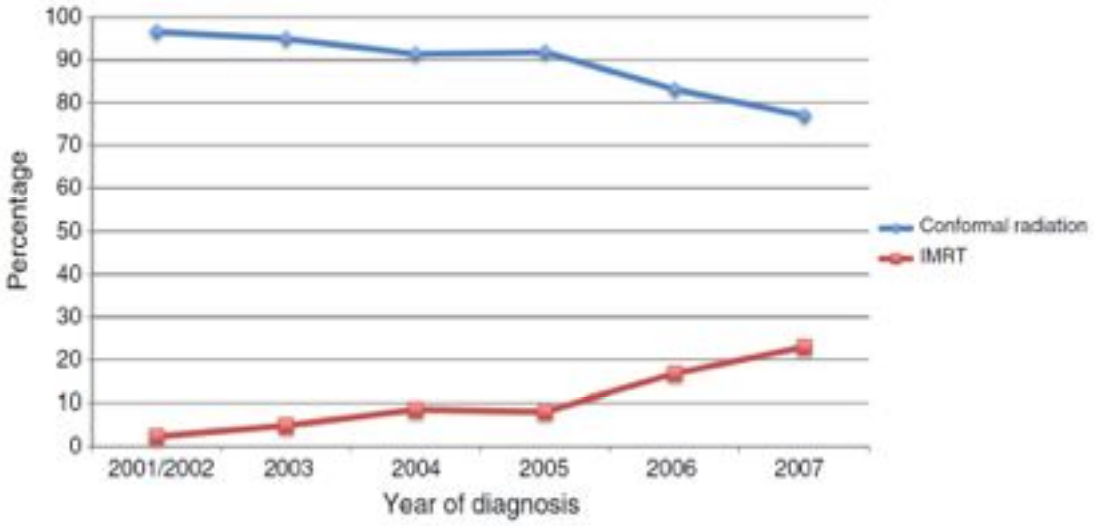
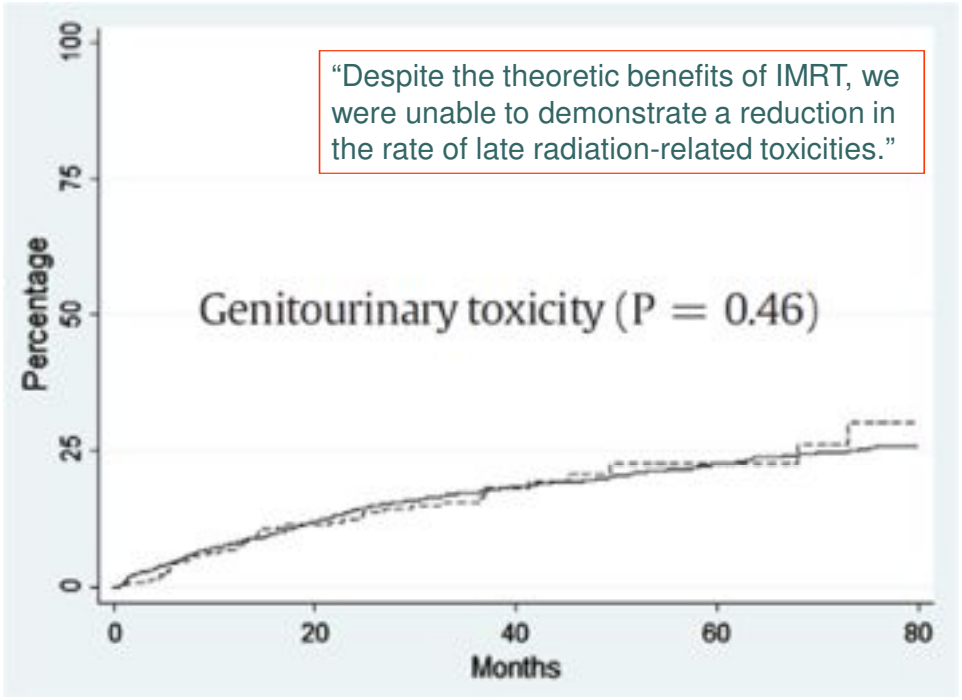


Fig. 1. Pelvic radiotherapy stratified by year of treatment for women with uterine cancer.

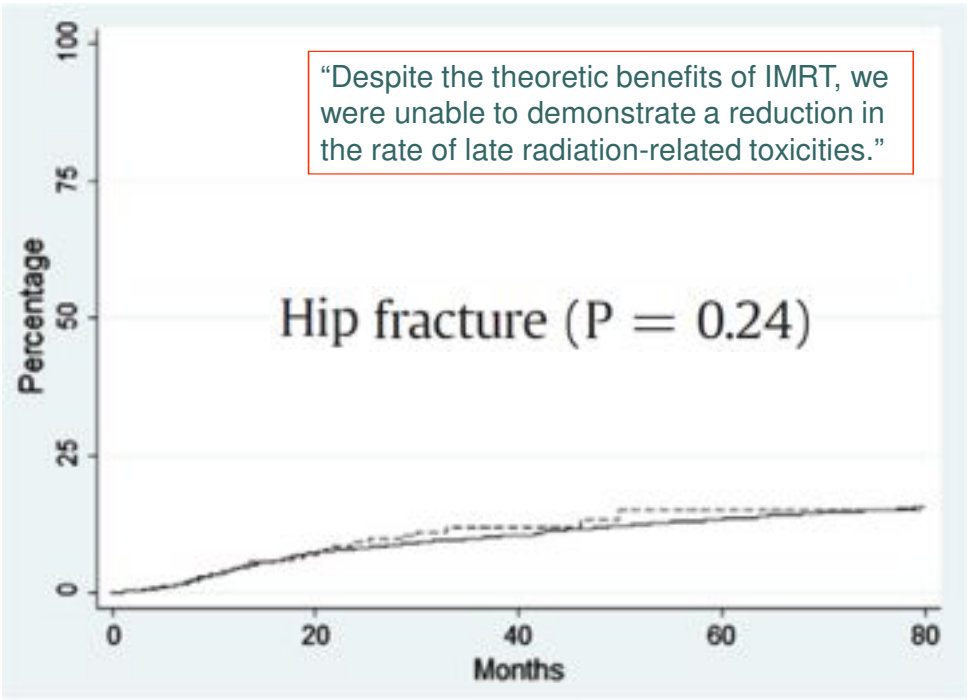
Gynecologic Oncology 130 (2013) 43–48

Uptake and outcomes of intensity-modulated radiation therapy for uterine cancer



Gynecologic Oncology 130 (2013) 43–48

Uptake and outcomes of intensity-modulated radiation therapy for uterine cancer



Gynecologic Oncology 130 (2013) 43–48

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

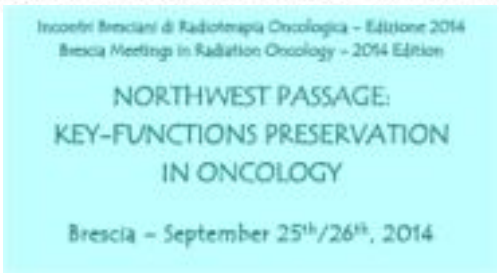
International Journal of Radiation Oncology biology • physics

Table 2 Crude incidences of individual vaginal symptoms before treatment (N = 588)

Grade	Vaginal stenosis	Vaginal dryness	Vaginal mucositis	Vaginal bleeding
G0	560 (95%)	547 (93%)	533 (91%)	174 (30%)
G1	6 (1%)	21 (4%)	34 (6%)	291 (49%)
G2	4 (1%)	2	3 (1%)	86 (15%)
G3	0	N.A.	0	17 (3%)
G4	N.A.	N.A.	0	2
G5	N.A.	N.A.	0	0
Missing	18 (3%)	18 (3%)	18 (3%)	18 (3%)

Abbreviation: N.A. = not applicable.

Surgery/radiotherapy/chemotherapy interactions and treatment damage: the case of gynaecologic cancer
R. Santoni



1 - Different classifications of treatment related complications prevent a comparison of different papers (Surgeons, Surgeons supporting neoadiuvant CHT, Very Aggressive Surgeons, Reliable Radiation Oncologists who try to cure patients)
2 –Urunary tract dysfunction incidence has not considerably decreased during the latest years in spite of some statements of the literature
3 – The use of combined treatment with RT, CHT and Surgery may Increase the frequency of late side effects, but in the literature this information is missing
4 – A considerable effort in the past decades led to the Franco-Italian glossary of side effects after treament of gynaecolog tumors, but its terms of classification differ fron those we use (**RTOG**, **LENT-SOMA etc)**
5 – More clinical good sense and less rigid Guidelines may help to reduce side effects.