SICCR
Società Italiana di Chirurgia Colo-Rettale

2° ITER FORMATIVO IN COLOPROCTOLOGIA
VERCELLI, 15 DICEMBRE 2008

DANNI FUNZIONALI POST RADIOTERAPIA PELVICA

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La radioterapia (RT) rappresenta una modalità di trattamento delle neoplasie pelviche (retto, prostata, ginecologiche) utilizzata da sola o in combinazione con la chirurgia e/o la chemioterapia con finalità adiuvante o neoadiuvante

La RT è spesso associata a farmaci chemioterapici radiosensibilizzanti e radiopotenzianti

FATTORI PREDISPONENTI

- Sensibilità individuale
- Diabete e ipertensione arteriosa (alterazioni del microcircolo)
- Pregressa chirurgia addominale e pelvica, pregressa flogosi pelvica (fissità grosso e piccolo intestino)
- Chemioterapia (5-FU, actinomicina D, metotrexate, doxorubicina)
- Bambini, pazienti magri, carnagione chiara
- Errori tecnici (sovradosaggio, sovrapposizione dei campi)

ASPETTI ANATOMO-PATOLOGICI

- Iniziale danno mucoso (interferenza con la cinetica cellulare, estensione del danno dose-dipendente)
- Necrosi delle cellule delle cripte con focali ulcerazioni, marcata reazione infiammatoria (infiltrato di PMN)
- "Cronicizzazione" del danno anche dopo la sospensione del trattamento (ialinizzazione sottomucosa; deposito fibroblasti; endoarterite obliterante delle arteriole intraparietali e teleangectasie sottomucose; fibrosi, fissurazioni e ulcerazioni della muscolare; ialinosi diffusa della sierosa)
- Ulcerazione, perforazione, necrosi ischemica della parete, fistole, stenosi

ASPETTI CLINICI - 1

- Vi può essere una sintomatologia acuta durante o subito dopo la RT
- Vi può essere un periodo di latenza più o meno lungo (settimane, mesi, anni)
- Talora l'esordio clinico è rappresentato da un disturbo cronico

ASPETTI CLINICI - 2

FASE ACUTA

- Nausea, vomito, crampi addominali, diarrea (lesioni del piccolo intestino piuttosto che del colon)
- Proctite da raggi (mucosa eritematosa, facilmente sanguinante, priva del normale pattern vascolare)

ASPETTI CLINICI - 3

FASE CRONICA

- Teleangectasia mucosa: lesione endoscopica patognomonica
- Disturbi legati alla sede e all'entità del danno (malassorbimento, diarrea, talora pseudo-ostruzione)
- Quadri clinici legati al danno morfologico (ostruzione, ulcere, emorragie, fistole, infarto, perforazione)

ASPETTI CLINICI - 4

- OCCLUSIONE: secondaria ad aderenze e fibrosi con formazione di stenosi (stenosi anastomotiche post resezione anteriore seguita da RT)
- ULCERAZIONI: secondarie a ischemia focale, possono essere superficiali o penetranti (fistole, perforazione -> peritonite), diffuse (diarrea mucosanguinolenta) o limitate (proctite) o isolate (ulcera solitaria)
- FISTOLE: secondarie a ulcere penetranti, interne o esterne (enterocutanee); la più frequente è la fistola retto-vaginale; biopsiare gli orifizi per escludere recidiva neoplastica
- INFARTO: raro ma spesso letale, secondario a endoarterite obliterante di vasi di calibro maggiore
- NEOPLASIE: rischio più elevato di carcinoma colorettale (follow up di almeno 10 anni), di 1-8 volte dopo RT pelvica, di 2-3.6 volte dopo RT per neoplasie ginecologiche

Sandler RS, Sandler DP. Radiation induced cancers of the colon and rectum: assessing the risk. *Gastroenterology* 1983

EFFETTI AVVERSI DELLA RADIOTERAPIA NEL TRATTAMENTO DEL CANCRO DEL RETTO

✓ La radioterapia, pre e postoperatoria, si è dimostrata efficace nel downstaging e downsizing così da ridurre il tasso di recidiva locale e aumentare la sopravvivenza nei pazienti affetti da cancro del retto

Bosset JF, Calais G et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results - EORTC 22921. *J Clin Oncol* 2005; 23: 5620-7

Stockholm Rectal Cancer Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. *Cancer* 1990; 66: 49-55

Gervaz PA, Wexner SD et al. Pelvic radiation and anorectal function: Introducing the concept of sphincter-preserving radiation therapy. *J Am Coll Surg* 2002; 195: 387-94

Martling AL, Holm T et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group. Basingstoke Bowel Cancer Research Project. *Lancet* 2000; 356: 93-6

Kapiteijn E, van de Velde CJ. The role of total mesorectal excision in the management of rectal cancer. *Surg Clin North Am* 2002; 82: 995-1007

✓ Gli effetti avversi possono essere precoci (tossicità acuta) e tardivi (complicanze tardive)

TOSSICITA' ACUTA - 1

✓ RCTs hanno mostrato un rischio raddoppiato (10-20%) di infezione perineale in pazienti sottoposti a RT preoperatoria

✓ Non vi è un aumento del tasso di deiscenza anastomotica nei pazienti operati per cancro del retto se non nei pazienti in scadenti condizioni

Påhlman L, Glimelius B et al. Pre- versus postoperative radiotherapy in rectal carcinoma: an interim report from a randomized multicentre trial. *Br J Surg* 1985; 72: 961-6

Stockholm Rectal Cancer Study Group. Short term preoperative radiotherapy for adenocarcinoma of the rectum: an interim analysis from a randomised multicentre trial. *Am J Clin Oncol* 1987; 10: 369-75

Swedish Rectal Cancer Trial. Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. *Br J Surg* 1993; 80: 1333-6

Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997; 336: 980-7

Kapiteijn E, Kranenbarg EK et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. *Eur J Surg* 1999; 165: 410-20

Sauer R, Becker H et al. Preoperative versus postoperative chemioradiotherapy for rectal cancer. *N Engl J Med* 2004; 351: 1731-40

TOSSICITA' ACUTA - 2

✓ Sono stati segnalati casi di neuropatia acuta con dolore gluteo e tendineo in pazienti sottoposti a RT preoperatoria "short-course"

Jansson-Frykholm GJ, Sintorn K et al. Acute lumbosacral plexopathy during and after preoperative radiotherapy of rectal adenocarcinoma. *Radiother Oncol* 1996; 38: 121-30

COMPLICANZE TARDIVE

Riguardano principalmente la funzione intestinale, urinaria e la sfera sessuale

Altre complicanze interessano l'apparato cardiovascolare (fenomeni tromboembolici) e osteoarticolare (fratture pelviche e di femore)

Danni funzionali post radioterapia pelvica

Functional Outcome in Irradiated and Surgery-Alone Groups

	Irradiated Group (n = 84)	Surgery-Alone Group (n = 87)
Frequency		
Stools/week (median, range)	20.5 (2–98)	10.0 (2–50)*
>Four emptyings per day	17 (20)	7 (8)†
Loperamide use	7 (8)	6 (7) NS
Urgency		
Deferring time (median, range)‡	5.0 (0–120)	10.0 (0–300)§
Toilet dependence	25 (30)	5 (6)§
Tenesmus	23 (28)	19 (22) NS
Emptying difficulties		
Emptying difficulties	44 (52)	31 (36)†
Early return to toilet‖	57 (69)	38 (45)*
Enema usage	1 (1)	2 (2) NS
Incontinence		
Incontinence of gas	57 (68)	44 (51)†
Incontinence of loose stool	42 (50)	21 (24)§
Incontinence of solid stool	12 (14)	3 (3)†
Nocturnal leakage	12 (14)	7 (8) NS
Use of pad	41 (49)	19 (22)§
Perineal excoriation	23 (27)	6 (7)§
Sensory function		
Ability to release flatus without stool incontinence	73 (87)	82 (94) NS
Discrimination between gas and stool	64 (76)	70 (80) NS

NS = nonsignificant.
Figures are number of patients and (percentages) unless otherwise indicated.
* $P < 0.01$.
† $P < 0.05$.
‡ Time possible to defer defecation (min).
§ $P < 0.001$, chi-squared test or Mann-Whitney U test.
‖ Need to return to toilet within one hour of defecation.

DISFUNZIONI INTESTINALI

Volume 41 — Diseases of the COLON & RECTUM — Number 5
MAY 1998
ORIGINAL CONTRIBUTIONS

Preoperative Irradiation Affects Functional Results After Surgery for Rectal Cancer

Results from a Randomized Study

Michael Dahlberg, M.D.,* Bengt Glimelius, M.D., Ph.D.,†
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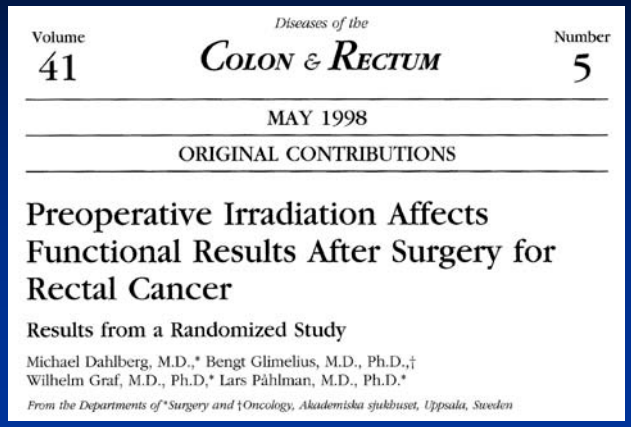
*From the Departments of *Surgery and †Oncology, Akademiska sjukhuset, Uppsala, Sweden*

Risultati funzionali

DISFUNZIONI INTESTINALI



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Grado di soddisfazione percepito dai pazienti

	Irradiated group (n=84)	Surgery-alone group (n=87)	P value
Excellent	12 (14)	28 (32)	<0.01
Good	43 (51)	47 (54)	
Acceptable	23 (28)	12 (14)	
Bad	6 (7)	0	

DISFUNZIONI INTESTINALI

Evaluation of Preoperative and Postoperative Radiotherapy on Long-Term Functional Results of Straight Coloanal Anastomosis

Daniel R. Nathanson, M.D.,* N. Joseph Espat, M.D.,* Garrett M. Nash, M.D.,* Matthew D'Alessio, M.D.,* Howard Thaler, Ph.D.,† Bruce D. Minsky, M.D.,‡ Warren Enker, M.D.,§ Douglas Wong, M.D.,* Jose Guillem, M.D.,* Alfred Cohen, M.D.,‖ Philip B. Paty, M.D.*

*From the Departments of *Surgery, †Biostatistics, and ‡Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, New York, §Continuum Cancer Centers of New York and the Beth Israel Medical Center, New York, New York, and ‖Lucille Markey Cancer Center, University of Kentucky, Lexington, Kentucky*

Dis Colon Rectum 2003;46:888-894.

	Pre-RT group (n=39)	Post-RT group (n=11)	No RT group (n=59)	P value
Frequency (≥3BM/24 hr)	41%	91%	41%	<0.01
Clustering (2 BM in 30 min, ≥1episode/wk)	46%	82%	36%	<0.02
Continence of solid stool (incontinent: leakage of solid stool, ≥1episode/wk)	92%	82%	78%	NS
Patient satisfaction with bowel function	72%	55%	75%	NS

DISFUNZIONI INTESTINALI

VOLUME 23 · NUMBER 25 · SEPTEMBER 1 2005
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Late Side Effects of Short-Course Preoperative Radiotherapy Combined With Total Mesorectal Excision for Rectal Cancer: Increased Bowel Dysfunction in Irradiated Patients—A Dutch Colorectal Cancer Group Study

K.C.M.J. Peeters, C.J.H. van de Velde, J.W.H. Leer, H. Martijn, J.M.C. Junggeburt, E. Klein Kranenbarg, W.H. Steup, T. Wiggers, H.J. Rutten, and C.A.M. Marijnen

Table 2. Clinical and Pathologic Patient Characteristics in Both Treatment Arms

Characteristic	RT + TME (n = 306) No. of Patients	%	TME (n = 291) No. of Patients	%	Total No. (N = 597)
Age, years					
Mean	63.06		61.60		
Range	34-86		27-84		
Sex					
Male	199	65	170	58	369
Female	107	35	121	42	228
Tumor location, cm*					
≤ 5	86	28	95	33	181
5.1-10.0	123	40	109	38	232
≥ 10.1	96	32	87	30	183
Operation type					
APR	91	30	86	30	177
LAR	200	65	197	68	397
Hartmann	15	5	8	3	23
TNM stage					
0	8	3	10	3	18
I	140	46	123	42	263
II	84	28	82	28	166
III	74	24	76	26	150
Stoma present					
No	177	58	185	64	362
Yes	129	42	106	36	235
Follow-up, years					5.09
Median	4.98		5.18		
Range	2.6-7.6		2.7-7.5		

Abbreviations: RT, radiotherapy; TME, total mesorectal excision; APR, abdominoperineal resection; LAR, low anterior resection.
*For one irradiated patient, tumor location could not be determined.

Table 1. Questions Asked to Assess Bowel, Stoma, and Urinary Function

Bowel function
Mean bowel frequency at day and night
Anal blood and mucus loss
Fecal incontinence at day and night
Pad wearing as a result of fecal incontinence
Stoma function
Peristomal skin irritation
Stoma smell
Stoma bleeding
Stoma leakage
Painful stoma
Noisy stoma
Urinary function
Mean urinary frequency at day and night
Hematuria
Dysuria
Urinary incontinence
Use of pads for urinary incontinence
Need to urinate again within 2 hours
Stream hesitation
Difficulty postponing urination
Weak urinary stream
Impact of bowel and urinary dysfunction on
Work or household activities
Activities outside the house like shopping or paying visits
Social activities like theater or cinema visiting
Satisfaction with bowel, stoma, and urinary function

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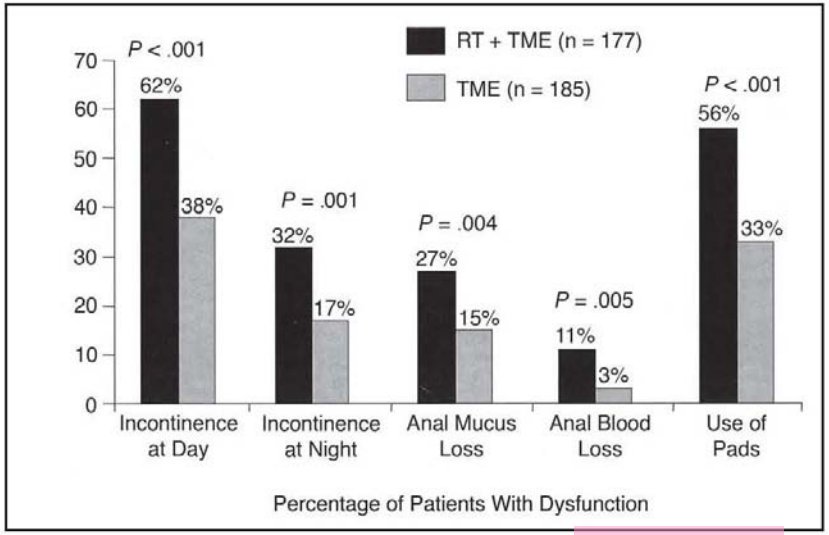

Fig 1. Bowel function in eligible patients at risk without a stoma. RT, radiotherapy; TME, total mesorectal excision.

Disfunzioni globali

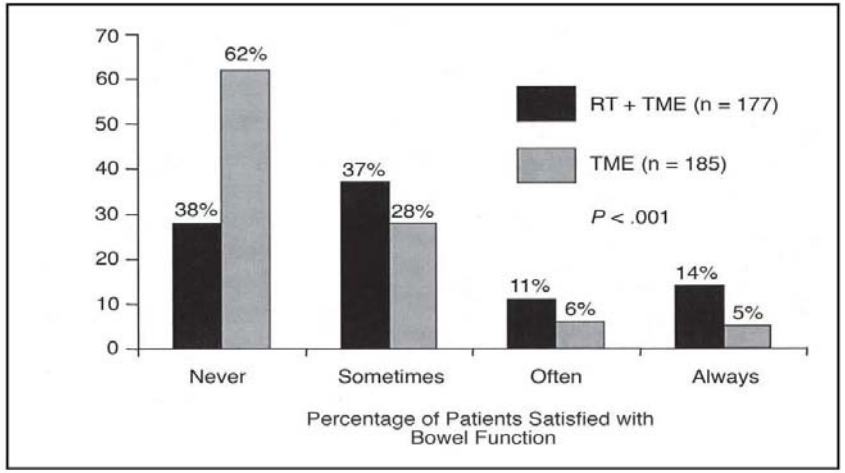

Fig 2. Degree of fecal incontinence at day in patients at risk without a stoma who reported some degree of fecal incontinence (n = 362). Sometimes was defined as once a week or less; often was defined as more than once a week; and always was defined as every day. RT, radiotherapy; TME, total mesorectal excision.

Grado di incontinenza

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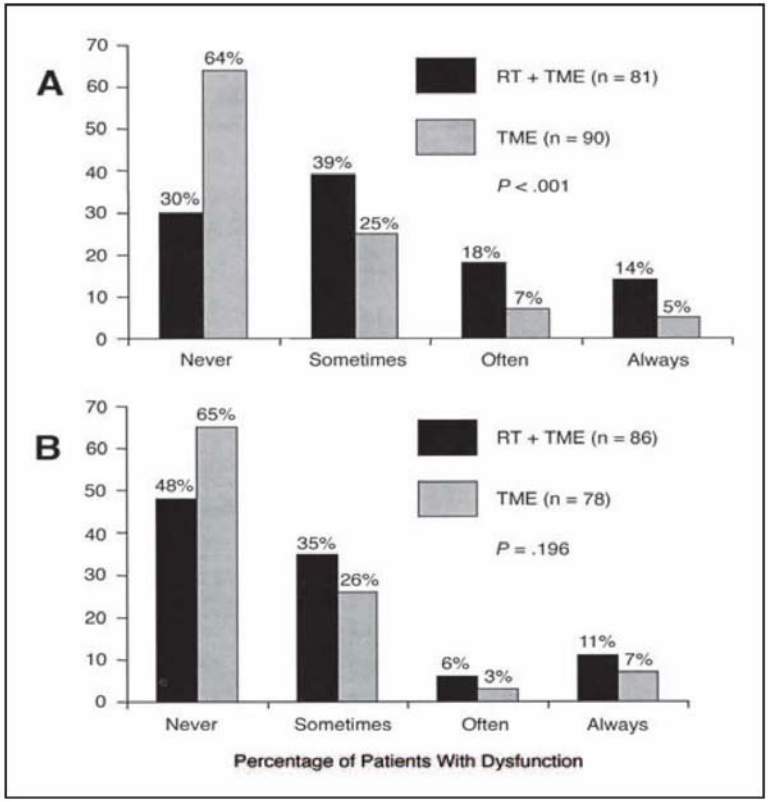

Fig 3. Degree of fecal incontinence at day in patients at risk without a stoma who reported some degree of fecal incontinence (n = 362). (A) Patients without a stoma with tumors between 5.1 and 10 cm from the anal verge. (B) Patients without a stoma with tumors between 10.1 and 15 cm from the anal verge. Sometimes was defined as once a week or less; often was defined as more than once a week; and always was defined as every day. RT, radiotherapy; TME, total mesorectal excision.

5-10 cm

Grado di incontinenza a seconda della distanza della neoplasia dal margine anale

10-15 cm

DISFUNZIONI SESSUALI

Havenga K, Enker WE et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. *J Am Coll Surg* 1996; 182: 495-502

54 donne (12 RT-pre, 9 RT-post, 33 TME)

86% sessualmente attive

85% normale lubrificazione vaginale
91% in grado di raggiungere il climax

DISFUNZIONI SESSUALI

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Impact of Short-Term Preoperative Radiotherapy on Health-Related Quality of Life and Sexual Functioning in Primary Rectal Cancer: Report of a Multicenter Randomized Trial

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Table 2. Patients Characteristics for the Evaluated Group

	PRT+ (n = 497)		PRT− (n = 493)		
	No. of Patients	%	No. of Patients	%	*P*
Median age, years	64.0		64.0		.61
Sex					.58
Male	318	64.0	307	62.3	
Female	179	36.0	186	37.7	
Operation type					.08
LAR	323	65.0	334	67.7	
APR	147	29.6	146	29.6	
Hartmann	27	5.4	13	2.6	
TNM stage					.5
0/I	203	40.8	169	34.3	
II	149	30.0	140	28.4	
III	145	29.2	157	31.8	
Distance to anal verge					.36
0-5	139	28.0	159	32.3	
5-10	210	42.3	189	38.3	
10-15	145	29.2	143	29.0	
Unknown	3	0.6	2	0.4	

Abbreviations: PRT+, radiotherapy and surgery; PRT−, surgery only; LAR, low anterior resection; APR, abdominoperineal resection.

La RT peggiora la funzione sessuale nelle femmine ($p<0.001$) e nei maschi ($p<0.004$), i quali presentano, rispetto ai non irradiati, disordini dell'eiaculazione ($p<0.002$) e un deterioramento a lungo termine della capacità erettile ($p<0.001$)

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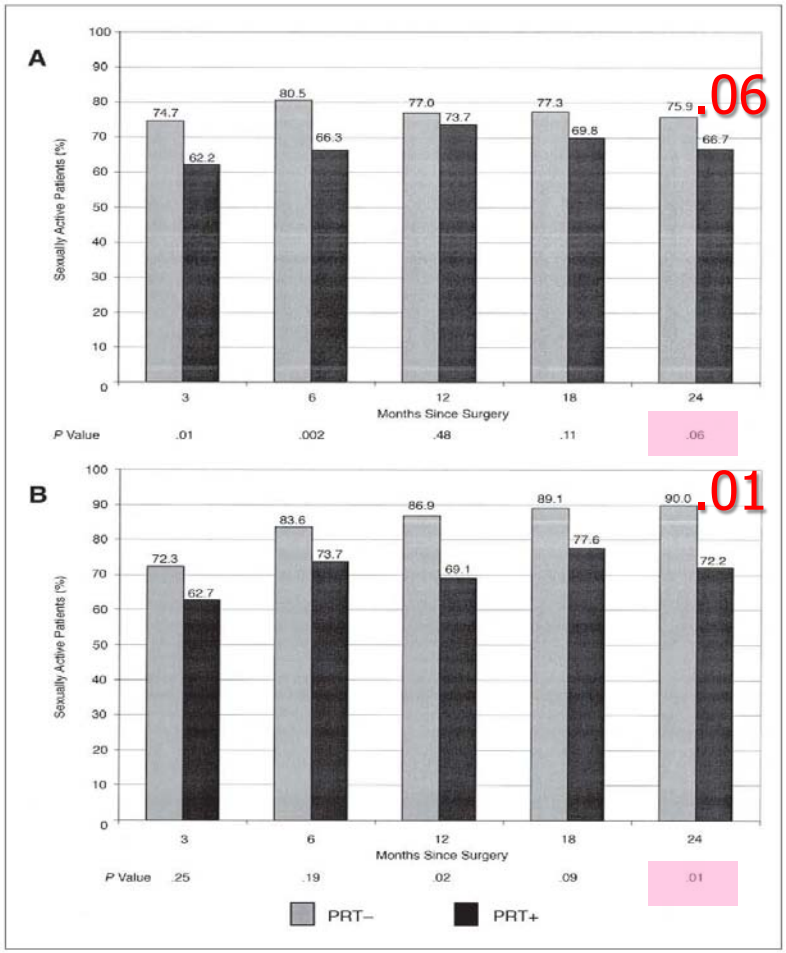

Fig 2. Sexual activity of (A) male and (B) female patients who were sexually active preoperatively. *P* values represent the difference between the randomization arms at each time point.

♂

81% PRT+
78% PRT-

53% PRT+
50% PRT-

♀

DISFUNZIONI URINARIE

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Table 4. Urinary Function

Factor	RT+TME (n = 306) No. of Patients	RT+TME (n = 306) %	RT+TME (n = 306) No. Missing	TME (n = 291) No. of Patients	TME (n = 291) %	TME (n = 291) No. Missing	P
Median urinary frequency at day, No.	6.21		21	5.97		11	.270
Median urinary frequency at night, No.	1.51		6	1.41		4	.260
Hematuria	5	2	7	2	1	8	.286
Dysuria	27	9	7	22	8	8	.585
Urinary incontinence	118	39	6	109	38	3	.711
Use of pads for incontinence	67	57	5	62	57	5	.983
Sensation of uncompleted bladder emptying	139	47	13	134	48	9	.985
Need to urinate again within 2 hours	203	70	16	195	71	18	.710
Stream hesitation	131	45	15	136	49	13	.315
Difficulty in postponing urination	152	53	17	141	52	17	.788
Weak urinary stream	158	55	17	144	52	15	.552
Need to push or strain to urinate	77	26	13	92	33	12	.079
Satisfaction about urinary function			6			5	.903
Satisfied	207	68		194	68		
Neutral	74	24		75	26		
Unsatisfied	19	6		17	6		

Abbreviations: RT, radiotherapy; TME, total mesorectal excision.

Incontinenza: perdita involontaria di urina almeno una volta a settimana

CONCLUSIONI

- La RT ha un ruolo fondamentale nel trattamento multimodale del cancro del retto ma produce effetti avversi a lungo termine, sia prima che dopo la chirurgia
- Questi effetti, che coinvolgono le funzioni fisiologiche e, in senso più ampio, la vita di relazione e la qualità di vita, vanno considerati il "prezzo" da pagare agli indubbi benefici
- Una corretta informazione dei pazienti circa le possibilità di effetti avversi della RT, oltre a quelli che la chirurgia di per sé produce, è di primaria importanza
- Il miglioramento delle modalità di erogazione della RT potranno consentire una maggior efficacia clinica insieme a una riduzione della dose erogata e della tossicità a carico dei tessuti circostanti (es. tomoterapia elicoidale)
- Studi di biologia molecolare (test di radiosensibilità) potranno consentire di selezionare i pazienti "resistenti" alla RT evitando così l'insorgenza di effetti avversi a fronte di benefici oncologicamente trascurabili

GRAZIE PER L'ATTENZIONE...