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Tossicità nei trattamenti dell'apparato gastroenterico

PROCTITE E RETTORRAGIA: PRESIDI DI PREVENZIONE E TRATTAMENTO DELLE TOSSICITÀ

Francesca De Felice

PROCTITE E RETTORRAGIA

- ~4,500 pazienti → RT per tumore addome/pelvi
  - Dettagli operativi Lazio-Abruzzo-Molise (2015)

Common Toxicity Criteria for acute radiation injury

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Proctitis	None	Increased stool frequency, occasional blood-streaked stools or rectal discomfort (including hemorrhoids) not requiring medication	Increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	Increased stool frequency/ diarrhea requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads	Perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)

75%

RTOG/EORTC late radiation morbidity

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	No changes	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea or colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, or fistula

20%

PROCTITE E RETTORRAGIA

- Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO)
  - Linee guida basate sull'evidenza
    - prevenzione e trattamento mucosite gasto-intestinale
      - 2004, 2007, **2012**
        - **146 articoli inclusi**

I Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power).

II Evidence obtained from at least 1 well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power).

III Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case-control series.

IV Evidence obtained from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.

V Evidence obtained from case reports and clinical examples.

PROCTITE E RETTORRAGIA

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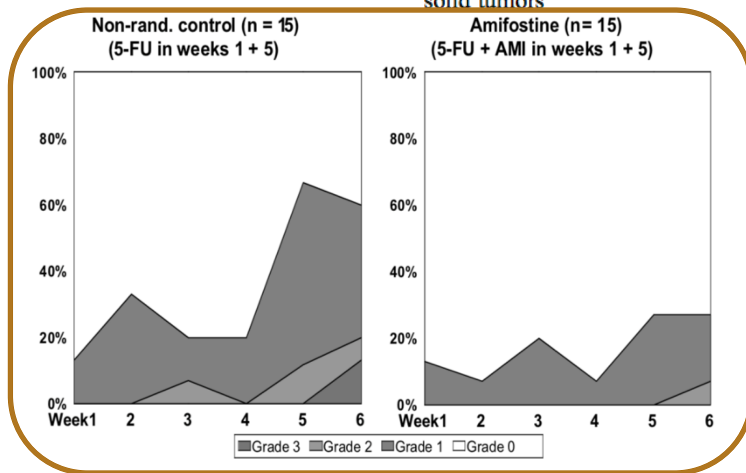
Recommendation	Reserved for guidelines that are based on level I or level II evidence.
Suggestion	Used for guidelines that are based on level III, level IV, and level V evidence; this implies panel consensus regarding the interpretation of this evidence.
No guideline possible	Used when there is insufficient evidence on which to base a guideline; this implies 1) that there is little or no evidence regarding the practice in question, or 2) that the panel lacks consensus on the interpretation of existing evidence.

Lalla et al. Cancer 2014

PROCTITE E RETTORRAGIA

- Raccomandazione – prevenzione –
  - Amifostina (composto aminotiolo)
    - Tiolo WR-1605 e disulfide WR-33278 → Effetto cito-protettivo: lega radicali liberi; accelera riparazione DNA

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author, year (citation number from reference list) of papers reviewed	Overall level of evidence	Guideline determination
Amifostine	IV	Either chemotherapy only or concomitant chemotherapy/ radiotherapy for various solid tumors	P	Delioukina, 2002 [42] Movsas, 2005 [18] Komaki, 2005 [19] Garcia-Manero, 2002 [43] Arquette, 2002 [44] Leong, 2003 [45] Antonadou, 2003 [46] Capelli, 2000 [47] Dunst, 2000 [48] Awasthy, 2001 [49] Werner-Wasik, 2001 [50] Tsavaris, 2005 [51]	II	The panel suggests the use of amifostine to reduce oesophagitis induced by concomitant chemotherapy and radiotherapy in patients with nonsmall cell lung carcinoma The panel recommends that amifostine should be administered intravenously at a dose of ≥340 mg/m^2 prior to radiotherapy to prevent radiation proctitis

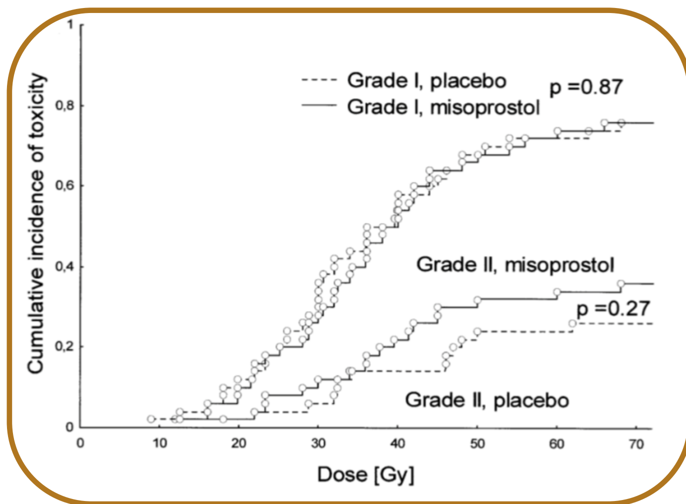


Lalla et al. Cancer 2014
Dunts et al. Strahlenther Onkol 2000
Kligerman et al. Int J Radiat Oncol Biol Phys. 1988
Savoye et al. Int J Radiat Biol. 1997

PROCTITE E RETTORRAGIA

- Raccomandazione – prevenzione –
  - Misoprostolo (analogo prostaglandina E1)
    - Δ flusso ematico nella mucosa → effetto citoprotettivo

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author, year (citation number from reference list) of papers reviewed	Overall level of evidence	Guideline determination
Misoprostol	Rectal enema	Standard-dose radiotherapy for prostate cancer	P	Hille, 2005 [24] Kertesz, 2009 [25] Khan, 2000 [106]	I	The panel recommends against the use of misoprostol suppositories for prevention of acute radiation-induced proctitis in men treated with standard radiotherapy for prostate cancer



Peak incidence of patients toxicity symptoms

Variable	Placebo (% per treatment group)	Misoprostol (% per treatment group)
Rectal bleeding†		
None	43 (86)	34 (68)
Blood-tinged bowel movements	7 (14)	14 (28)
Significant blood with bowel movements	0	2 (4)

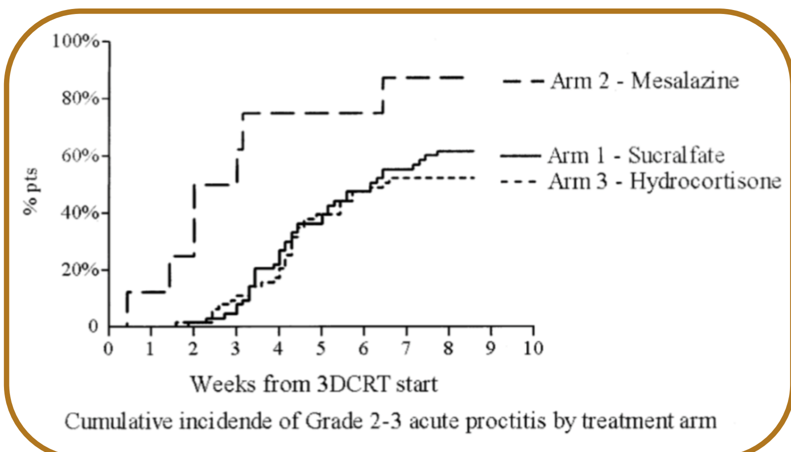
† $p = 0.03$

Lalla et al. Cancer 2014
Hille et al. Int. J. Radiation Oncology Biol. Phys. 2005

PROCTITE E RETTORRAGIA

- Suggerimento – trattamento –
  - Sucralfato (saccarosio + idrossido di alluminio)
    - Aderisce alle cellule mucosa → effetto citoprotettivo
    - Δ sintesi Pg, EGF → promuove riparazione mucosa

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author, year (citation number from reference list) of papers reviewed	Overall level of evidence	Guideline determination
Sucralfate	Enema	Standard-dose radiotherapy for various solid tumors	T	Kochhar, 1990 [139] O'Brien, 1997 [140] Kochhar, 1999 [141] Melko, 1999 [142] O'Brien, 2002 [143] Gul, 2002 [144] Sanguineti 2003 [145] Chun, 2004 [146]	III	The panel suggests that using sucralfate enemas may help manage chronic radiation-induced proctitis in patients with rectal bleeding



Cumulative incidende of Grade 2-3 acute proctitis by treatment arm

Lalla et al. Cancer 2014
Sanguineti et al. Strahlenther Onkol 2003

PROCTITE E RETTORRAGIA

- Suggerimento – trattamento –
  - Ossigeno iperbarico
    - Effetto angiogenetico
    - ø crescita batteri e produzione tossine

Name of agent	Route of administration	Cancer type and treatment modality	Indication	Author, year (citation number from reference list) of papers reviewed	Overall level of evidence	Guideline determination
Hyperbaric oxygen	n/a	Standard-dose radiotherapy for various solid tumors	T	Kernstine, 2005 [88] Jones, 2006 [89] Fink, 2006 [90] Huddy, 2006 [91] Dall'Era, 2006 [92] Ginius, 2006 [93]	IV	The panel suggests that hyperbaric oxygen therapy is an effective way to treat radiation-induced proctitis

Response	No. Pts (%)
Bleeding:	25
Resolved	12 (48)
Improved	7 (28)
Unchanged	5 (20)
No data	1 (4)
Fecal urgency:	4
Resolved	2
Improved	1
Unchanged	0
No data	1
Pain:	8
Resolved	0
Improved	6
Unchanged	1
No data	1
Rectal ulcer:	14
Resolved	2
Improved	5
Unchanged	6
No data	1
Overall response:	27
Good	10 (37)
Partial	8 (30)
No change	9 (33)

Treatment outcomes following hyperbaric therapy

Symptoms/functions	No. of patients (*n*)	Complete resolution (*n*)	Lent/Soma down grading (*n*)	No response (*n*)	Progression (*n*)
Bleeding	9	4	3	1	1
Pain/discomfort	5	3	1	1	
Diarrhea	5	1	3	1	

Lalla et al. Cancer 2014
Dall'Era et al. J Urol. 2006
Jones et al. Radiother Oncol. 2006

PROCTITE E RETTORRAGIA

- Molte opzioni e modalità di trattamento
  - Terapia medica
  - Terapia endoscopica
  - Terapia chirurgica

  acuta e **cronica**

  !! Assenza di linee guida !!

  - Risultati contradditori
    - Miglioramento sintomi
    - Nessun beneficio, peggioramento sintomi

Grodsky et al. Clinics in Colon and Rectal Surgery 2015

PROCTITE E RETTORRAGIA

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute	No changes	Increased frequency, change in bowel habits, or rectal discomfort not requiring medications or analgesics	Diarrhea requiring parasympatholytic drugs, mucous discharge not necessitating sanitary pads, abdominal or rectal pain requiring analgesics	Diarrhea requiring parenteral support, severe bloody or mucous discharge necessitating sanitary pads, abdominal distention	Acute or subacute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or diversion
Late	No changes	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding	Moderate diarrhea or colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis, perforation, or fistula

- Terapia medica
  - Anti-infiammatori
    - Sulfasalazina (sulfapiridina)
      - Ø sintesi acido folico batterico → azione batteriostatica
    - Mesalazina (acido 5-aminosalicilico)
      - Ø ciclossigenasi → riduce stimolo flogistico persistente
    - Cortisone
    - Studio prospettico, randomizzato, doppio cieco [37 pz.]
      - Sulfasalazina orale 3 g/die + prednisone microclismi 20 mg x 2/die versus sucralfato microclismi 2 g x 2/die + placebo orale (4 settimane)
        - **sucralfato: miglior risposta clinica 71% vs 47% ($p < 0.05$)**

Grodsky et al. Clinics in Colon and Rectal Surgery 2015
Sahebnasagh et al. J Altern Complement Med. 2017
Kochhar et al. Dig Dis Sci 1991

PROCTITE E RETTORRAGIA

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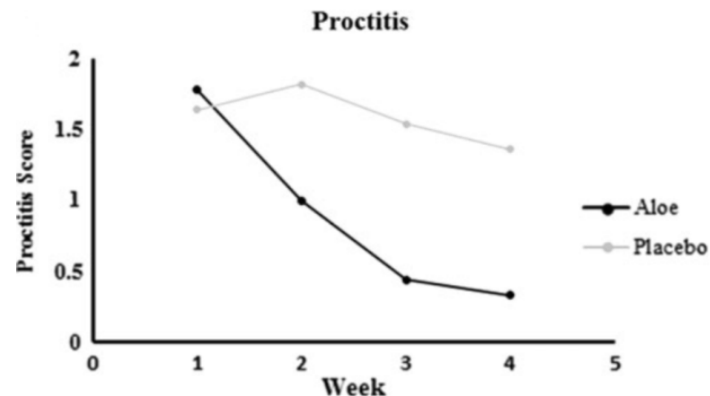
- Terapia medica
  - Aloe vera (gel)
    - Sembra Ø ciclossigenasi
    - Studio prospettico, randomizzato [20 pz]
      - Aloe vera + sulfasalazina 500 mg x 4/die versus placebo + sulfasalazina 500 mg x 4/die (4 settimane)
        - **Aloe vera: miglioramento sintomatologia**



Grodsky et al. Clinics in Colon and Rectal Surgery 2015
Sahebnasagh et al. J Altern Complement Med. 2017

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- Terapia medica
  - Agenti anti-ossidanti (Vitamina A, C, E)
    - Proprietà antiossidanti versus stress ossidativo
    - Studio prospettico, randomizzato, doppio cieco [17 pz.]
      - Vitamina A orale versus placebo (3 mesi)
        - **Vitamina A migliora sintomatologia**
  - Acidi grassi a catena corta (acido butirrico)
    - Prodotti dalla fermentazione di carboidrati non assorbibili a opera della flora batterica intestinale; fonte principale di energia dei colonociti
      - Δ proliferazione e differenziazione cellulare → effetto trofico
    - Studio prospettico, randomizzato, doppio cieco [19 pz.]
      - Acido butirrico microclisma versus placebo (5 settimane)
        - **Acido butirrico:** accelera processo di riparazione ma **no miglioramento significativo**
    - Studio prospettico, randomizzato, doppio cieco [15 pz.]
      - Acido butirrico microclisma versus placebo (2 settimane)
        - **Acido butirrico: no miglioramento significativo**

Grodsky et al. Clinics in Colon and Rectal Surgery 2015
Sahebnasagh et al. J Altern Complement Med. 2017
Ehrenpreis et al. Dis Colon Rectum 2005
Pinto et al. Dis Colon Rectum 1999

PROCTITE E RETTORRAGIA

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- Terapia endoscopica
  - Dilatazione endoscopica
  - Formalina (metanolo e formaldeide)
    - Cauterizzazione chimica dei tessuti → instillazione topica
    - Sclerosi dei vasi → ø sanguinamento
  - **Coagulazione argon plasma**
    - Facile, sicura, meno costosa
    - Energia elettrica trasmessa mediante argon gassoso ionizzato → essiccamento superficiale con ↑ resistenza elettrica
      - Δ distribuzione superficiale dell’effetto termico → coagulazione uniforme (non oltre 3 mm di profondità).
  - YAG laser (granato di ittrio e alluminio)
    - Vaporizzazione tessuto

Grodsky et al. Clinics in Colon and Rectal Surgery 2015

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- Terapia endoscopica
  - Sonda bipolare e termica
    - direttamente a contatto → punta della sonda continuamente pulita
  - Ablazione a radiofrequenza
  - Crioablazione

Grodsky et al. Clinics in Colon and Rectal Surgery 2015

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- Terapia chirurgica
  - Colostomia derivativa
    - Δ dolore, tenesmo, infezioni
    - Ø sanguinamento
  - Asportazione del retto
    - Sanguinamento persistente

Ultima opzione nella gestione della RT-proctite

Grodsky et al. Clinics in Colon and Rectal Surgery 2015

PROCTITE E RETTORRAGIA

- Limiti metodica rigorosa
  - No risposta esaustiva
    - No studi sufficientemente validi a supporto di interventi
  - Stimolo a condurre nuovi studi clinici

Terapia	Principio attivo	Posologia	Evidenza scientifica
PREVENZIONE			
Amifostina [Ethyol]	Tiofosfato organico	e.v. ≥ 340 mg/mq/die	RACCOMANDATO
Misoprostolo	Analogo PG E1		RACCOMANDATO
TRATTAMENTO			
Sucralfato [Antepsin]	Sale di alluminio	2 appl/die per 3 mesi	SUGGERITO
Vitamina A [Rovigon]	Anti-ossidante	1 cpr/die per 1 mese	SUGGERITO
Ossigeno iperbarico	O2 al 100% (2 atm)	Almeno 36 sedute	SUGGERITO