

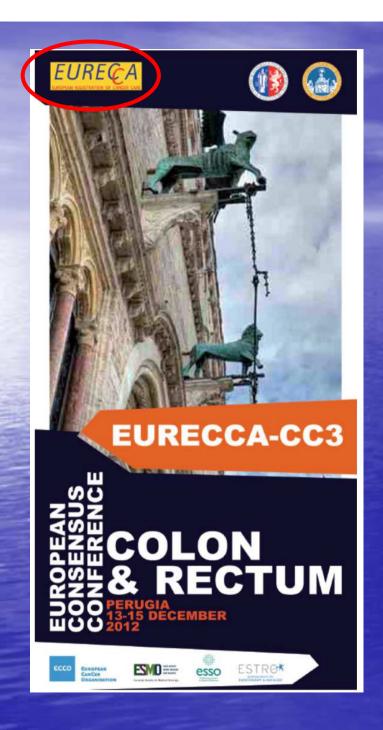
Il retto inizia a livello del corpo di S3, dove il crasso perde il suo mesentere.

Il peritoneo lo riveste nella porzione superiore, lateralmente e anteriormente, vicino alla giunzione con il sigma.

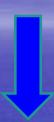
La porzione inferiore è priva di peritoneo.

- Colon and rectal cancer (CRC) are the second most common cancers (1 234 000 cases worldwide in 2008 according to GLOBOCAN and 447 000 in Europe in 2012) and cause many cancer related deaths each year (215 000 cases in Europe in 2012)
- Clinical audits were set up and several international trials were performed to improve loco regional control and survival of rectal cancer patients

- Overall, survival of patients with CRC has improved in most European countries over the past 20 years.
- In 1988-1990 survival of patients with rectal cancer was lower than that of patients with colon cancer.
- Survival of rectal cancer nowadays surpasses the survival of colon cancer (in North Europe, UK and central Europe).







- It supports the development of an European audit structure in order to improve the outcome of all patients with colon and rectal cancer.
- •To undertake this, the definition of treatment standards in colon and rectal cancer care in Europe are necessary.



variation in incidence, treatment and outcome of colon and rectal cancer worldwide

 outline the 'core quality treatment strategies' for colon and rectal cancer and reach consensus Dieta ricca in grassi animali e povera di fibre

I grassi assunti con la dieta stimolano la produzione di acidi biliari che influenzano la proliferazione dell'epitelio intestinale

Le fibre aumentano il volume fecale, riducono il tempo di transito nell'intestino e il pH delle feci

### **CONDIZIONI "PRECANCEROSE"**

Colite ulcerosa: RR 5-30:1

M. di Crohn

**Displasia- Polipi** 

FATTORI POTENZIALMENTE FAVORENTI CA

RT pelvica?

### Risk Assessment

Approximately 20% of cases of colorectal cancer are associated with familial clustering, 4,5 and first-degree relatives of patients with newly diagnosed colorectal adenomas<sup>6</sup> or invasive colorectal cancer<sup>7</sup> are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC])<sup>8,9</sup> and familial adenomatous polyposis (FAP).<sup>10</sup> Therefore, it is recommended that all patients with colorectal cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

Storia familiare	Stima del rischio (%)
Assenza di familiarità per cancro del colon-retto	2
Familiarità di I grado (1 familiare	e) 6
Un parente di I grado e due di II grado affetti da cancro al colon-retto	8
Un familiare di I grado affetto con età < 45 anni	10
Due familiari di I grado	17
HNPCC	70
FAP	100

HNPCC = tumori colo-rettali ereditari a carattere non polipoide; FAP = poliposi adenomatosa familiare



Se la malattia è diagnosticata in fase iniziale, la sopravvivenza a 5 anni è 90%, ma scende al 15%-20% se la diagnosi è tardiva

### CANCRO DEL COLON E DEL RETTO

### **SCREENING**

- 1. Categorie a rischio (es., colite ulcerosa con storia > 10 aa, anamnesi polipo, storia familiare poliposi, HNPCC): ricerca sangue occulto annuale (SOF), colonscopia o rettosigmoidoscopia + Rx clisma doppio mdc ogni 1-3 aa
- 2. Popolazione generale: SOF ogni 2 anni > 50 aa + rettosigmoidoscopia ogni 3-5 aa; costo esami aggiuntivi se SOF +, con predittività 10-20 %; ER (ruolo per altre neoplasie, bassa predittività)



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Colorectal Cancer Screening

Version 2.2012

NCCN.org

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

## **Rectal Cancer**

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## special article

# ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making

H. J. Schmoll<sup>1\*</sup>, E. Van Cutsem<sup>2</sup>, A. Stein<sup>3</sup>, V. Valentini<sup>4</sup>, B. Glimelius<sup>5,6</sup>, K. Haustermans<sup>7</sup>, B. Nordlinger<sup>8,9</sup>, C. J. van de Velde<sup>10</sup>, J. Balmana<sup>11</sup>, J. Regula<sup>12</sup>, I. D. Nagtegaal<sup>13</sup>, R. G. Beets-Tan<sup>14</sup>, D. Arnold<sup>3</sup>, F. Ciardiello<sup>15</sup>, P. Hoff<sup>16,17</sup>, D. Kerr<sup>18</sup>, C.H. Köhne<sup>19</sup>, R. Labianca<sup>20</sup>, T. Price<sup>21</sup>, W. Scheithauer<sup>22</sup>, A. Sobrero<sup>23</sup>, J. Tabernero<sup>24</sup>, D. Aderka<sup>25</sup>, S. Barroso<sup>26</sup>, G. Bodoky<sup>27</sup>, J. Y. Douillard<sup>28</sup>, H. El Ghazaly<sup>29</sup>, J. Gallardo<sup>30</sup>, A. Garin<sup>31</sup>, R. Glynne-Jones<sup>32</sup>, K. Jordan<sup>1</sup>, A. Meshcheryakov<sup>31</sup>, D. Papamichail<sup>33</sup>, P. Pfeiffer<sup>34</sup>, I. Souglakos<sup>35</sup>, S. Turhal<sup>36</sup> & A. Cervantes<sup>37</sup>

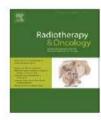
Radiotherapy and Oncology 92 (2009) 148-163



Contents lists available at ScienceDirect

### Radiotherapy and Oncology





European Rectal Cancer Consensus

Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2)

Vincenzo Valentini <sup>a,\*</sup>, Cynthia Aristei <sup>b</sup>, Bengt Glimelius <sup>e</sup>, Bruce D. Minsky <sup>f</sup>, Regina Beets-Tan <sup>i</sup>, Jose M. Borras <sup>c</sup>, Karin Haustermans <sup>d</sup>, Philippe Maingon <sup>j</sup>, Jens Overgaard <sup>k</sup>, Lars Pahlman <sup>l</sup>, Phil Quirke <sup>m</sup>, Hans-Joachim Schmoll <sup>h</sup>, David Sebag-Montefiore <sup>n</sup>, Irving Taylor <sup>o</sup>, Eric Van Cutsem <sup>g</sup>, Cornelius Van de Velde <sup>p</sup>, Numa Cellini <sup>a</sup>, Paolo Latini <sup>b</sup>, on behalf of the Scientific Committee <sup>1</sup>

## La clinica

	(%)
Calo ponderale	50
Alterazioni dell'alvo	60
Rettorragia	60
Anemia	4
Tenesmo	20

## DIAGNOSI

Anamnesi

Visita clinica con esplorazione rettale

Esami ematobiochimici

Markers

## DIFFUSIONE DELLA MALATTIA

Linfonodi regionali
 Profondità d'invasione
 Grado di differenziazione

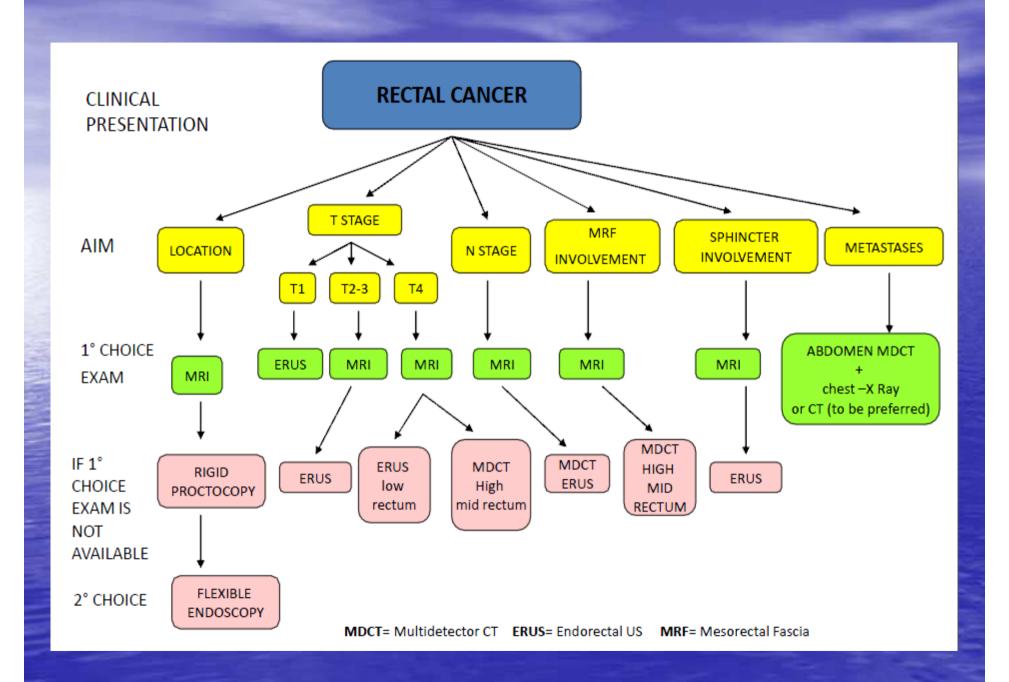
Matastasi ematogene Fegato Polmone

## Il drenaggio linfatico avviene principalmente in tre direzioni:

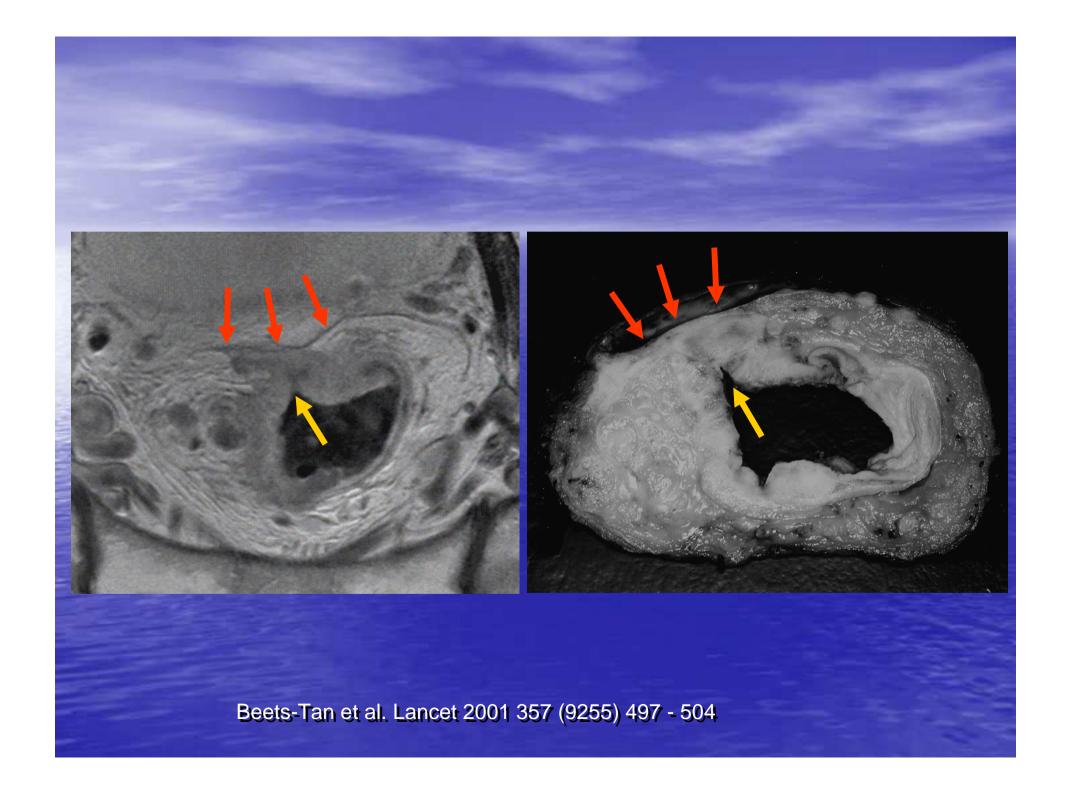
a. in senso craniale verso i linfonodi mesenterici inferiori e successivamente paraortici

b. in senso lateralmente nei linfonodi iliaci esterni

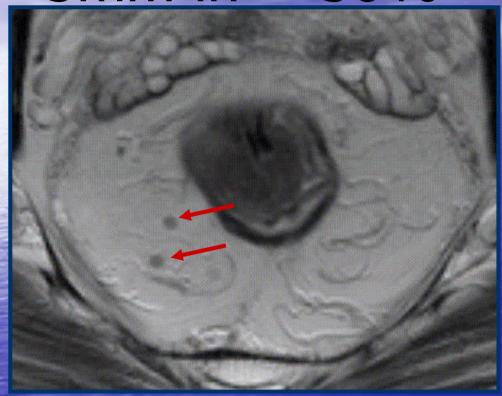
c. caudalmente nei linfonodi iliaci esterni e negli inguinali.

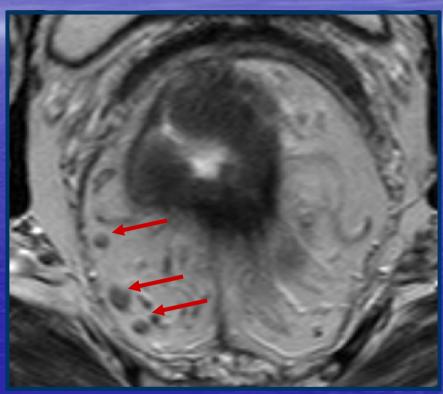


Location	Rigid proctoscopy	Flexible endoscopy	MRI
Low	Up to 5 cm	Up to 5 cm	Up to 4 cm
Mid	From >5 to 10 cm	From >5 to 10 cm	From >4 to 8 cm
High	From >10 up to 15 cm	From >10 up to 15 cm	From >8 up to 12 cm
Reference level	Anal verge	Anal verge	Anorectal junction



# metastatic nodes: less than Ø 5mm in > 50%





Dworak *et al. Surg Endos* 1989;3:96-9 Brown *et al. Radiology* 2003;227:371-7

#### Table 1. Definitions for T, N, M Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propriaª
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into the pericolorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneumb
- T4b Tumor directly invades or is adherent to other organs or structures b,c

### Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- NO No regional lymph node metastasis
- N1 Metastasis in 1-3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2-3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in four or more regional lymph nodes
- N2a Metastasis in 4-6 regional lymph nodes
- N2b Metastasis in seven or more regional lymph nodes

### Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

Table 2.	Anatomic	Stage/Prog	nostic G	roups	
Stage	T	N	M	Dukes*	MAC*
0	Tis	NO	MO	: <del>-</del>	0.000.00.000
1	T1	NO	MO	Α	A
	T2	NO	MO	Α	B1
HA	T3	NO	MO	В	B2
IIB	T4a	NO	MO	В	B2
IIC	T4b	NO	MO	В	B3
IIIA	T1-T2	N1/N1c	MO	C	C1
	T1	N2a	MO	C	C1
IIIB	T3-T4a	N1/N1c	MO	C	C2
	T2-T3	N2a	MO	C	C1/C2
	T1-T2	N2b	MO	С	C1
IIIC	T4a	N2a	MO	C	C2
	T3-T4a	N2b	MO	C	C2
	T4b	N1-N2	MO	C	C3
IVA	Any T	Any N	M1a	-	2
IVB	Any T	Any N	M1b	ascons Enc so we	- 10 AP

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

<sup>\*</sup>Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

## TERAPIA

Chirurgia

Radioterapia

Chemioterapia

Preoperatoria Postoperatoria

## **CHIRURGIA**

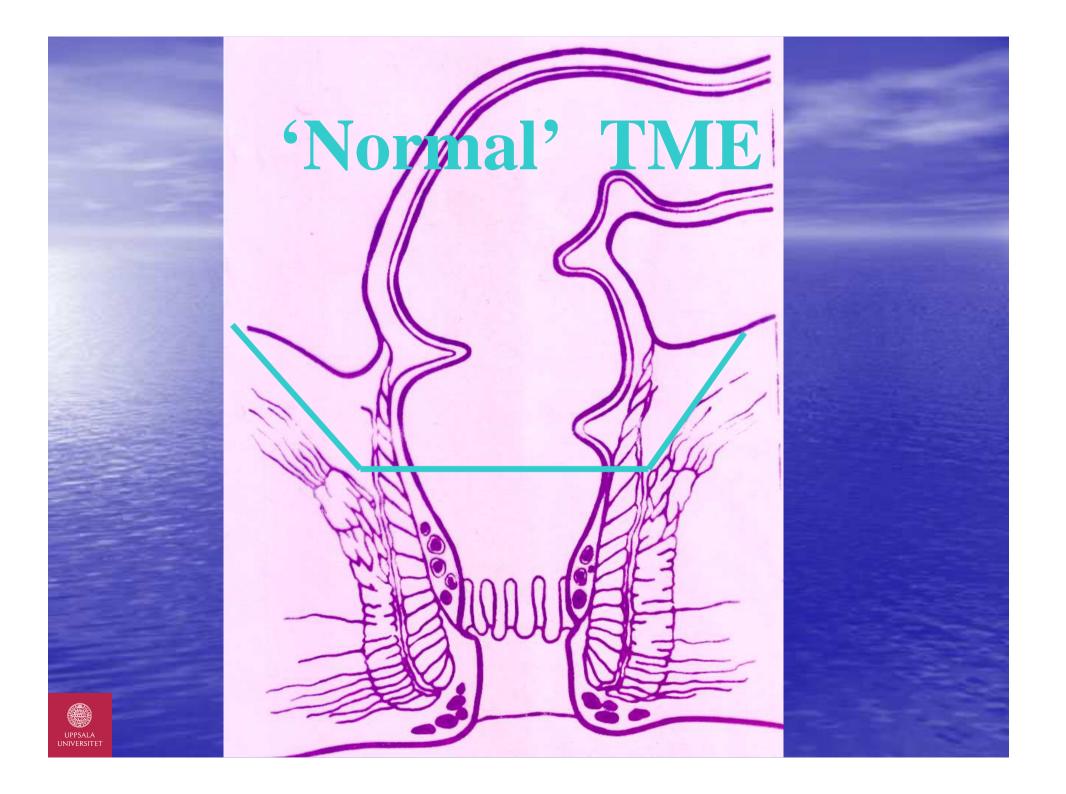
Il trattamento chirurgico rappresenta la terapia di scelta per la maggior parte dei pazienti

Resezione anteriore del retto

Resezione addomino-perineale

For lesions in the mid to upper rectum, a low anterior resection (LAR) extended 4-5 cm below the distal edge of the tumor, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required. Wide TME is recommended in order to facilitate adequate lymphadenectomy and improve the probability of achieving negative circumferential margins.

An abdominoperineal resection (APR) should be performed when the tumor directly involves the anal sphincter or the levator muscles. An APR is also necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy.<sup>93</sup>





## TME-Trial: RT+TME vs. TME



Local Failure at 5 years:

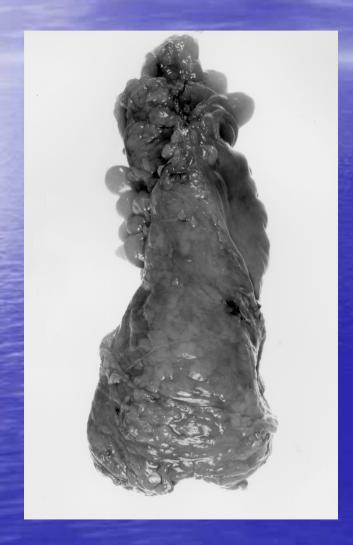
RT+TME: 5.6%

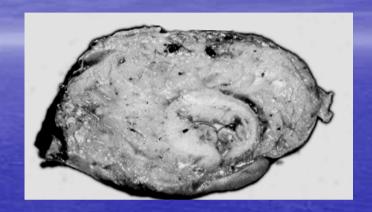
TME: 10.9%

p < 0.001

Kapiteijn E et al., N Engl J Med 2001;345: 638-46 Peeters K et al., Ann Surg 2007;246:693-701

## Quality of surgery: definitions



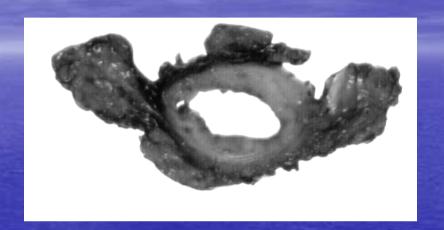


Complete mesorectum

No defect deeper than 5mm Smooth circumferential margin

## Quality of surgery: definitions





Incomplete mesorectum

Defects down onto muscularis Irregular circumferential margin

Con la sola chirurgia il rischio di recidiva locale è compreso tra il 15% e il 70%

Fattori di rischio per recidiva locale sono a la presenza di metastasi linfonodali, il grado di infiltrazione, lo stato dei margini (CRM)

 Metastasi a distanza si osservano nel 30% dei casi

## •CANCRO DEL RETTO

### • TERAPIA

•Risultati Chirurgia

N-: 75% sopravv. a 5 aa

N+: 30% " " "

• Fallimenti locali

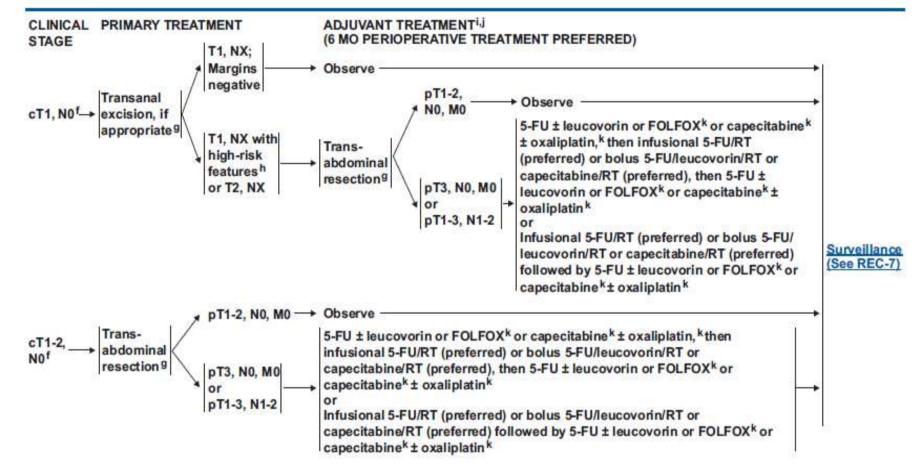
<u>T1-2 N0 M0: < 15%</u>

•T3 NO MO: 15 - 35%

•T3-4 o N1-2 M0: 45 - 70%

## Cancer Network\* Rectal Cancer

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fT1-2. N0 should be based on assessment of endorectal ultrasound or MRI.

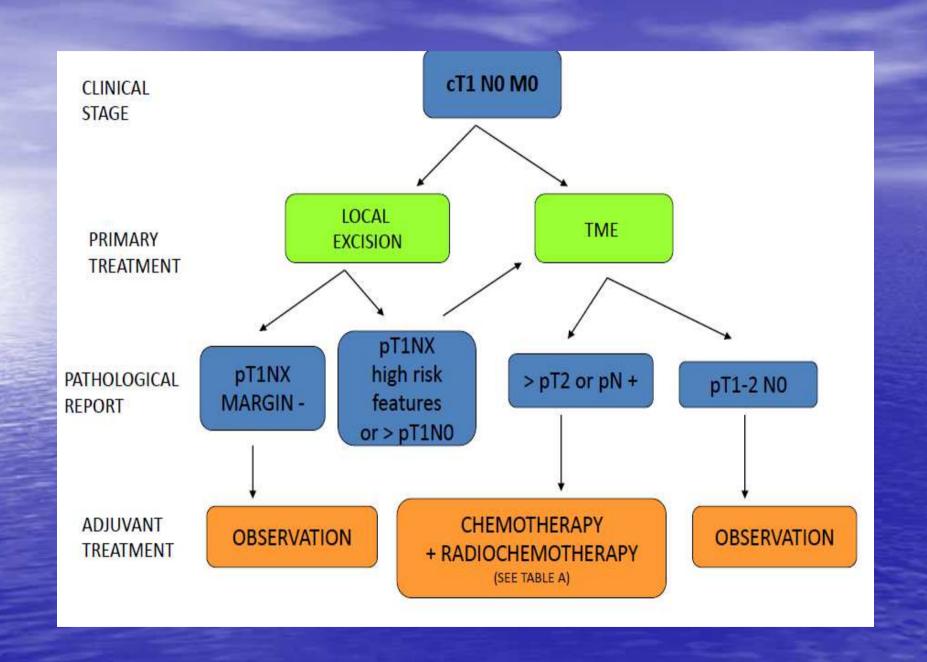
See Principles of Surgery (REC-B).

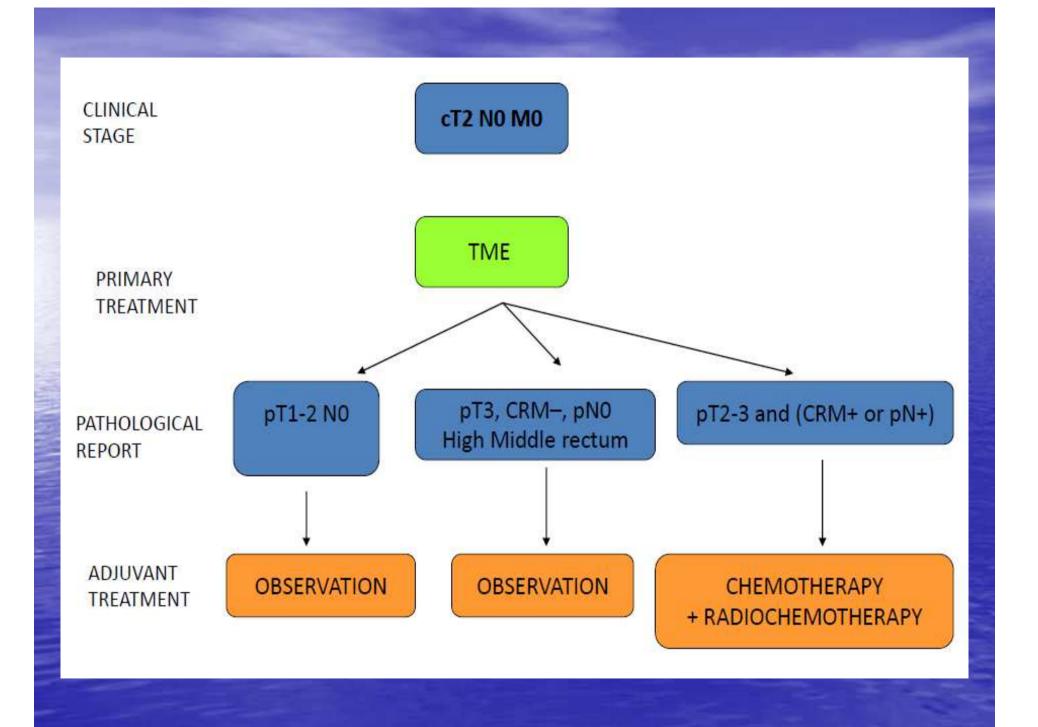
<sup>&</sup>lt;sup>h</sup>High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.

See Principles of Adjuvant Therapy (REC-C).

See Principles of Radiation Therapy (REC-D).

<sup>&</sup>lt;sup>k</sup>The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.





## RADIOTERAPIA + CHEMIOTERAPIA

L'impiego della RT postoperatoria ha ridotto il rischio di recidiva locale, ma non quello di metastasi a distanza



Associazione di RT e CT



**Trattamento Standard** 

# CT-RT PRE VS POSTOPERATORIA

- Riduce il rischio di diffusione perioperatoria di malattia
- Riduce la tossicità del trattamento
- Consente la preservazione dello sfintere
- Agisce su tessuti normalmente ossigenati
- Il vantaggio di un trattamento postoperatorio è che viene effettuato solo in pazienti a rischio di recidiva

# CT-RT PRE VS POSTOPERATORIA

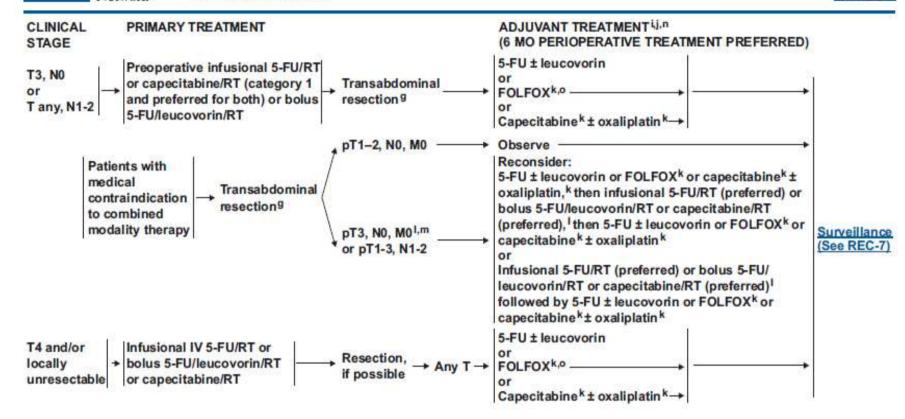
Preoperative versus postoperative radiation Several studies have compared the administration of radiation preoperatively versus postoperatively. 114,115 A large prospective. randomized trial from the German Rectal Cancer Study Group (the CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer. 114 Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs 13%; P = .006) and treatment-associated toxicity (27% vs 40%; P = .001), although overall survival was similar in the 2 groups. Long-term followup of this trial was recently published. 116 The improvement in local control persisted, with the 10-year cumulative incidence of local recurrence at 7.1% and 10.1% in the preoperative and postoperative treatment arms, respectively (P = .048). Overall survival at 10 years was again similar between the groups (59.6% and 59.9%, respectively; P = .85), as was disease-free survival and the occurrence of distant metastases.

# CT-RT PRE VS POSTOPERATORIA

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue. 114,115,117 First of all, reducing tumor volume may facilitate resection and increase the likelihood of a sphinctersparing procedure. Although some studies have indicated that preoperative radiation or chemoRT is associated with increased rates of sphincter preservation in rectal cancer patients, 114,115 this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer. 118,119 Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). One disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors that do not require adjuvant radiation. 114,120 Improvements in preoperative staging techniques, such as MRI or CT scans, have allowed for more accurate staging, but the risk of over-staging disease has not been eliminated. 113

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<sup>9</sup> See Principles of Surgery (REC-B).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Principles of Adjuvant Therapy (REC-C).

See Principles of Radiation Therapy (REC-D).

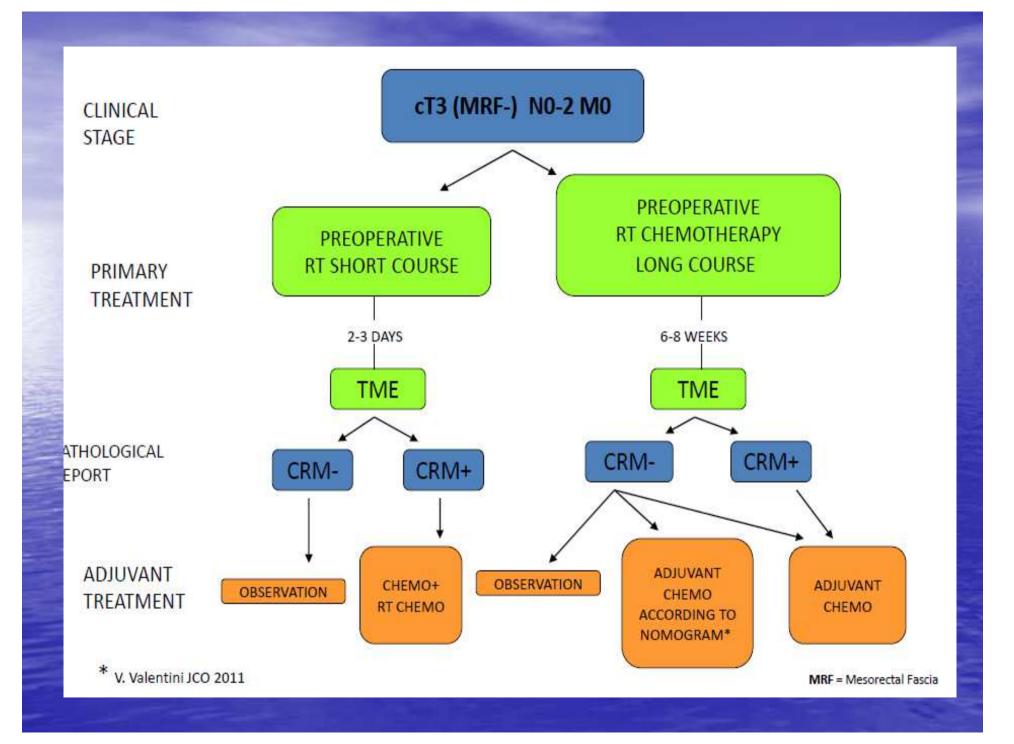
<sup>\*</sup>The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer.

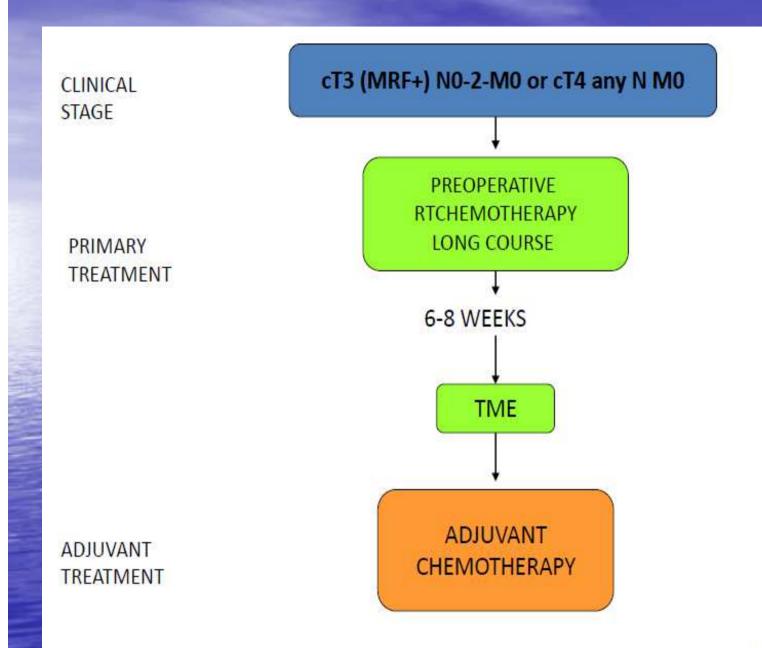
The use of agents other than fluoropyrimidines (eg, oxaliplatin) are not recommended concurrently with RT.

<sup>&</sup>lt;sup>m</sup>For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.

Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

OAn ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

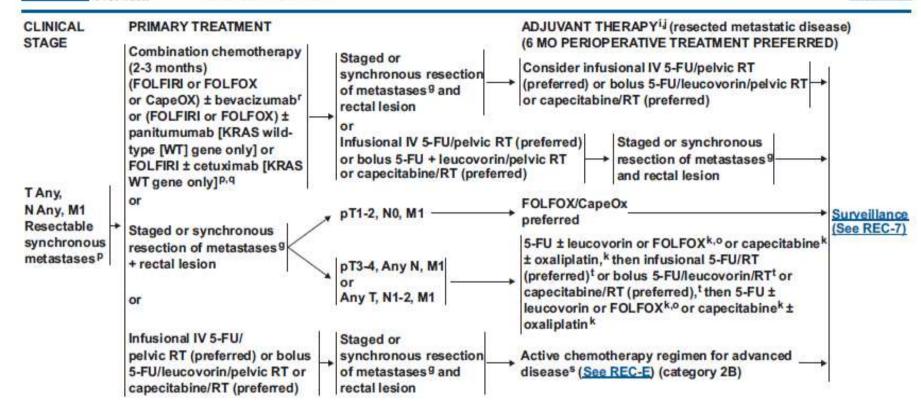




MRF = Mesorectal Fascia

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9See Principles of Surgery (REC-B).

See Principles of Adjuvant Therapy (REC-C).

See Principles of Radiation Therapy (REC-D).

There are insufficient data to guide the use of anti-EGFR therapy in the first-line setting with active chemotherapy based on BRAF V600E mutation status.

SFOLFOXIRI is not recommended in this setting.

<sup>1</sup>RT is only recommended for patients at increased risk for pelvic recurrence.

KThe use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.

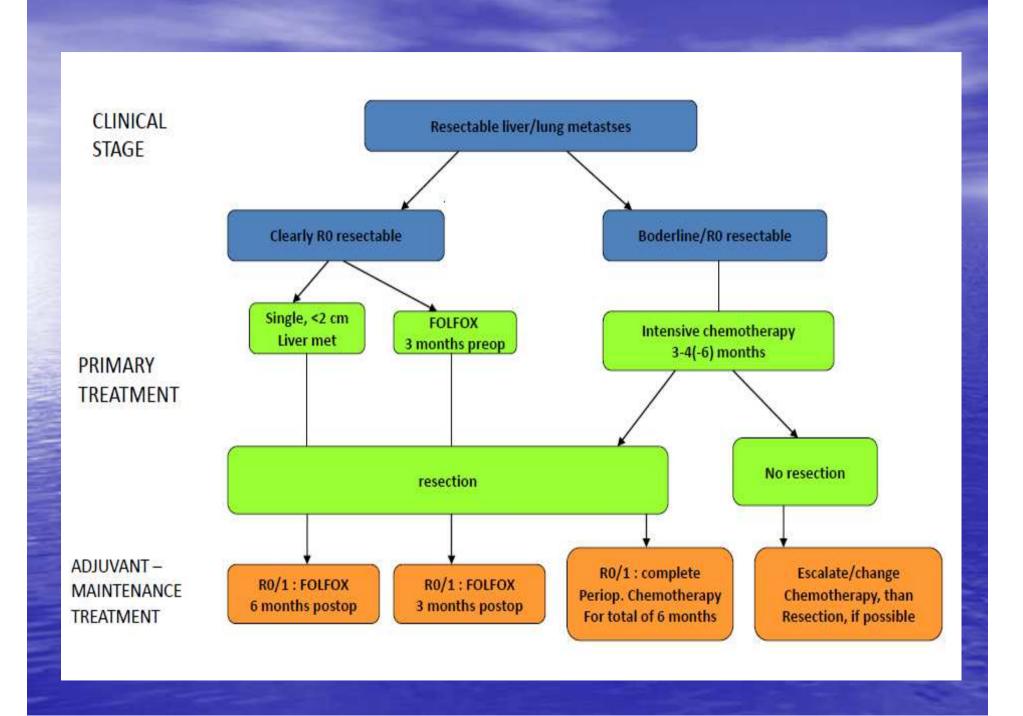
OAn ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

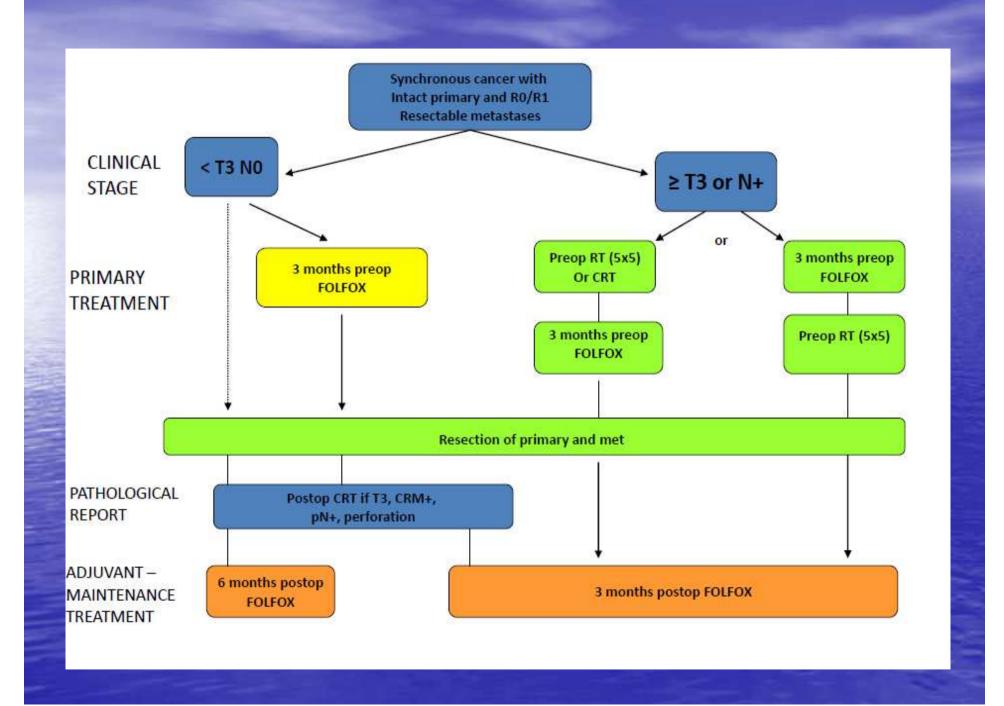
PDetermination of tumor KRAS (if KRAS non-mutated, consider BRAF testing).

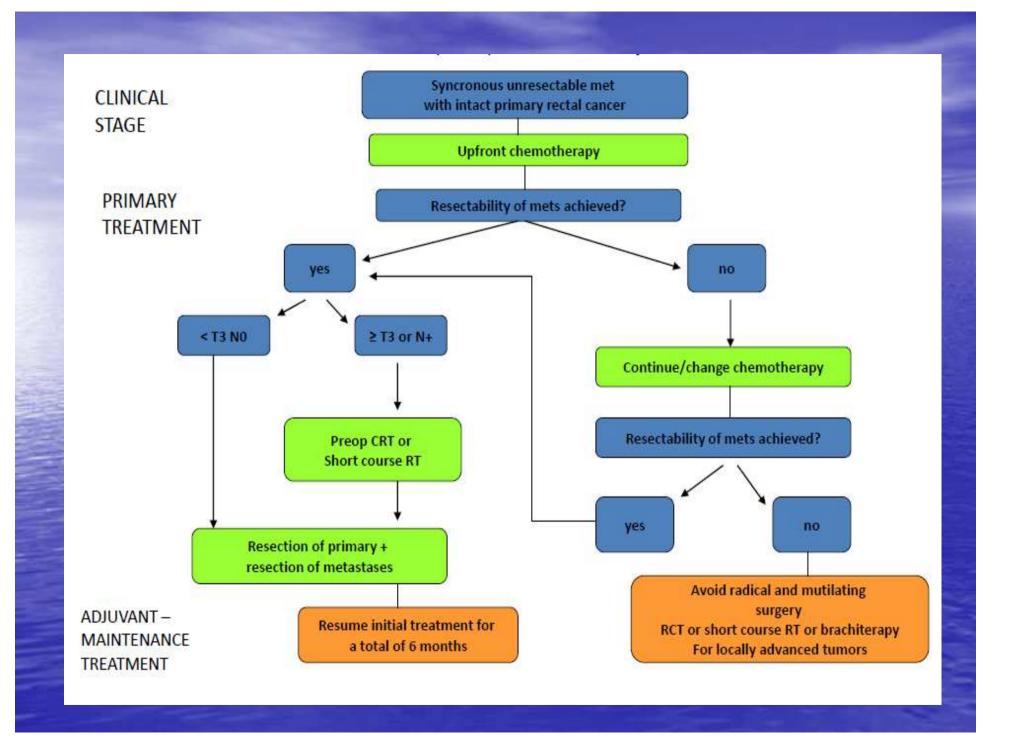
<u>See Principles of Pathologic Review (REC-A 5 of 6)</u> - KRAS and BRAF

Mutation Testing.

The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.







## Rectal Cancer

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Discussion

#### SURVEILLANCE\*

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA<sup>v</sup> every 3-6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions
- Chest/abdominal/pelvic CTf annually for up to 5 y for patients at high risk for recurrence<sup>x</sup>
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
- ➤ If advanced adenoma, repeat in 1 y
- If no advanced adenoma, y repeat in 3 y, then every 5 vz
- Consider proctoscopy every 6 mo x 5 y for patient status post LAR<sup>aa</sup>
- PET-CT scan is not routinely recommended
- See Principles of Survivorship (REC-F)

Serial CEA elevation or documented recurrence See Workup and Treatment (REC-8)

fCT should be with IV and oral contrast. Consider abd/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

VIf patient is a potential candidate for resection of isolated metastasis.

WDesch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23(33):8512-8519.

xCT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor; poorly differentiated tumors).

yVillous polyp, polyp >1 cm, or high-grade dysplasia.

<sup>&</sup>lt;sup>z</sup>Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130(6):1865-71.

aa Patients with rectal cancer should also undergo limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Optimal timing for surveillance is

### Comprehensive NCCN Guidelines Version 2.2013 **Rectal Cancer**

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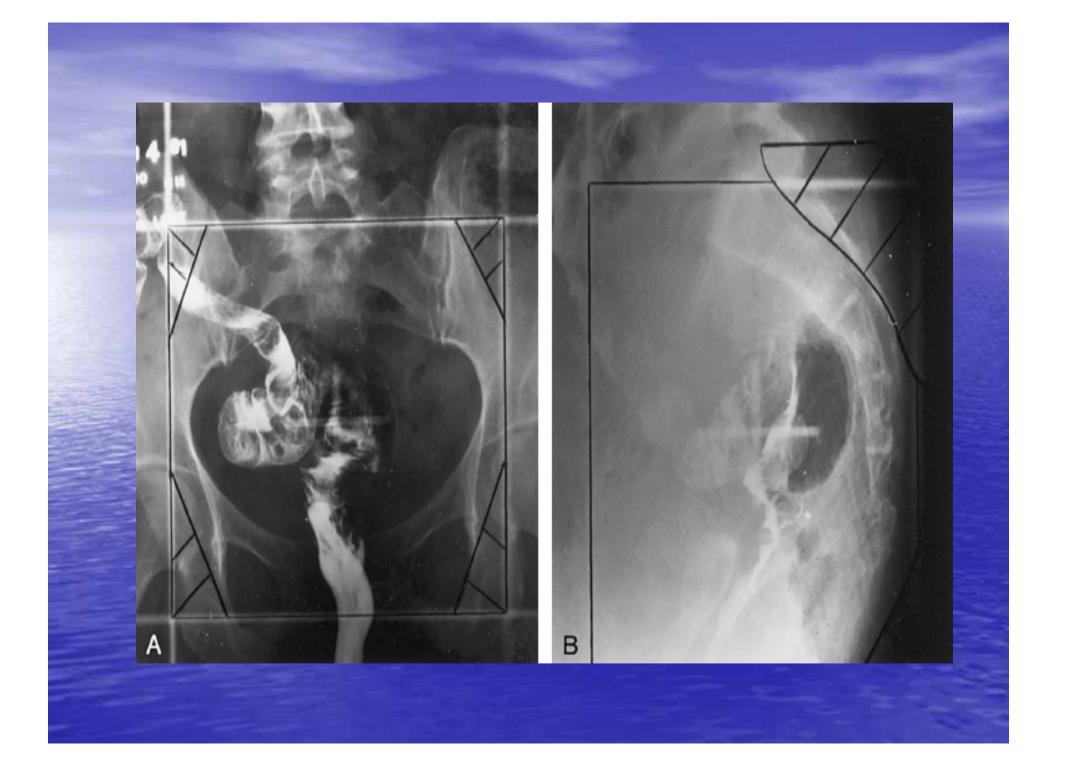
#### PRINCIPLES OF RADIATION THERAPY

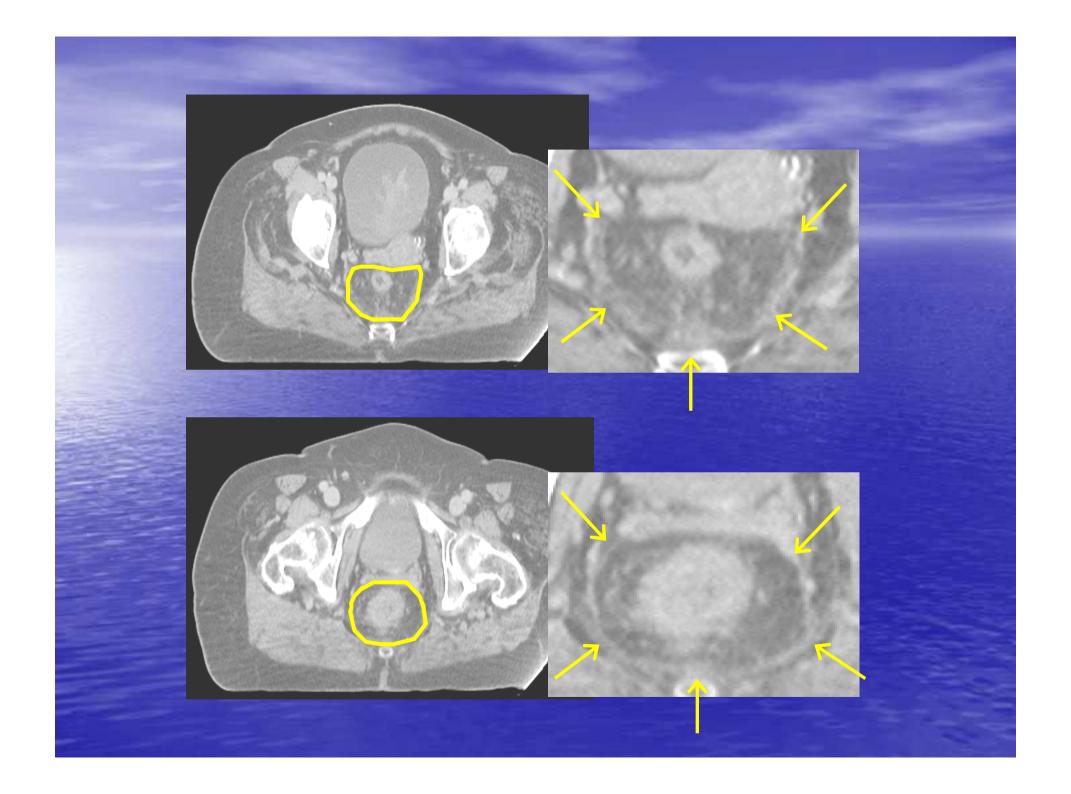
- Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including reirradiation of recurrent disease after previous radiotherapy.
- Radiation doses:
- > 45-50 Gy in 25-28 fractions to the pelvis.
- For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
- Small bowel dose should be limited to 45 Gy.
- Intraoperative radiation therapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10-20 Gy external beam radiation and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
- 5-fluorouracil-based chemotherapy should be delivered concurrently with radiation therapy.
- In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiotherapy, IMRT, or stereotactic body radiation therapy (SBRT). (category 3)
- Side effect management:

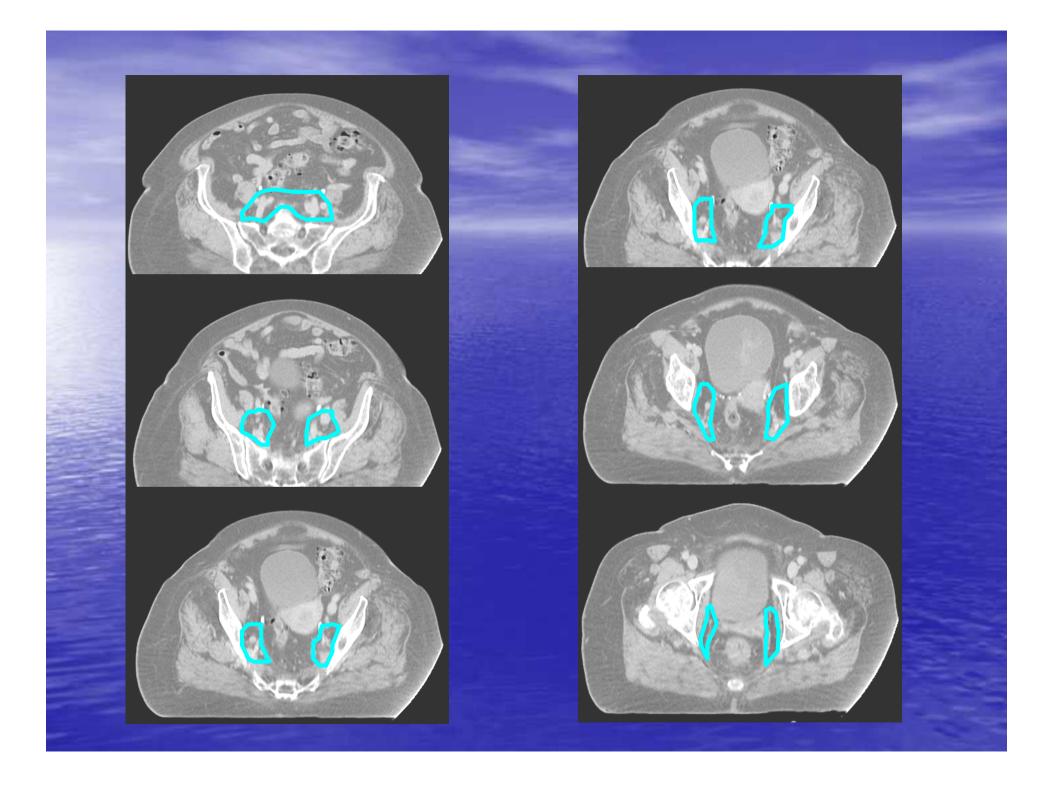
Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.

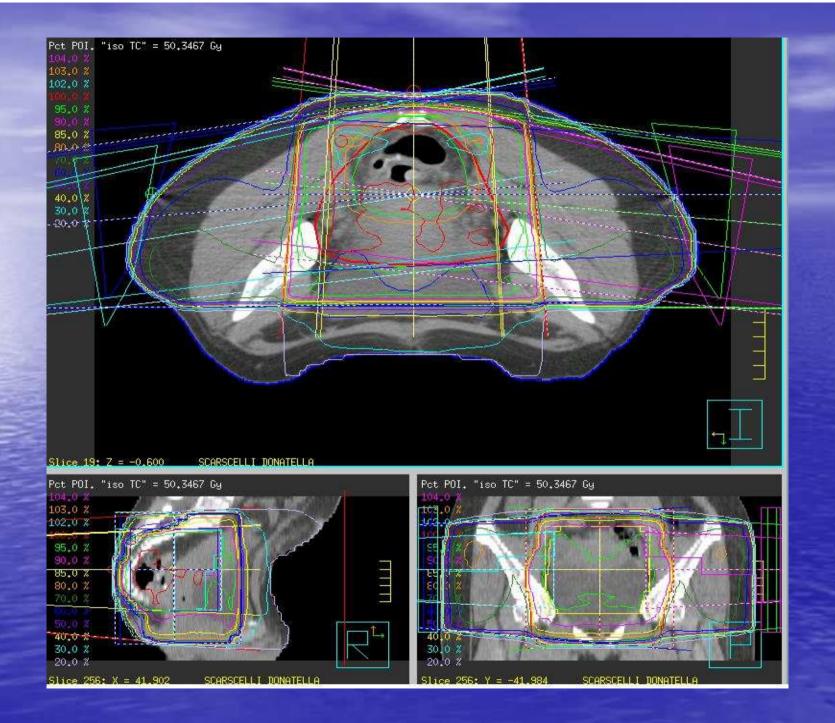
Male patients should be counseled on infertility risks and given information regarding sperm banking.

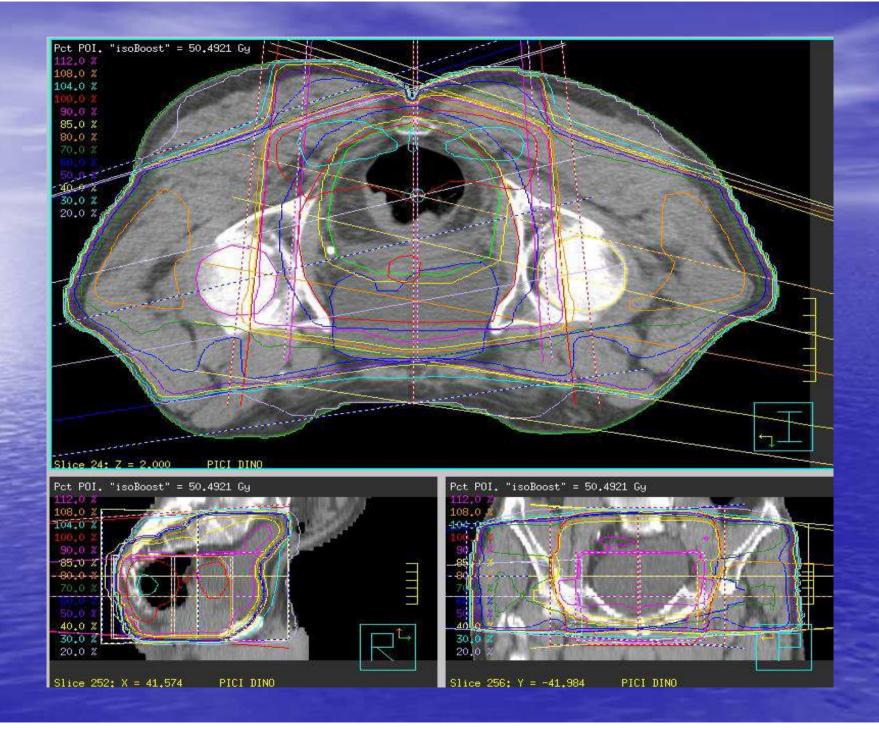
Female patients should be counseled on infertility risks and given information regarding oocyte, egg or ovarian tissue banking prior to treatment.

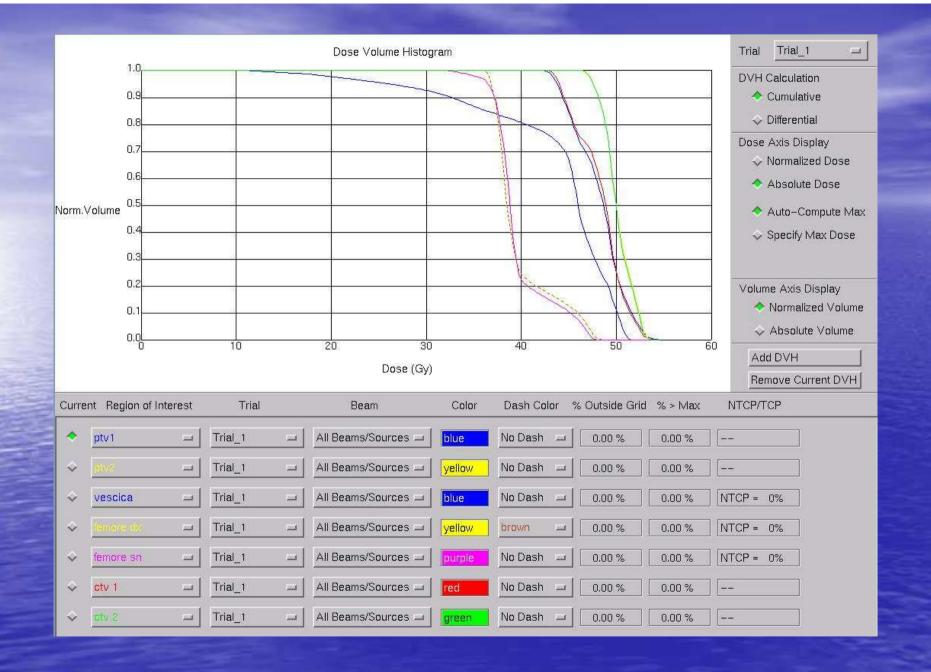


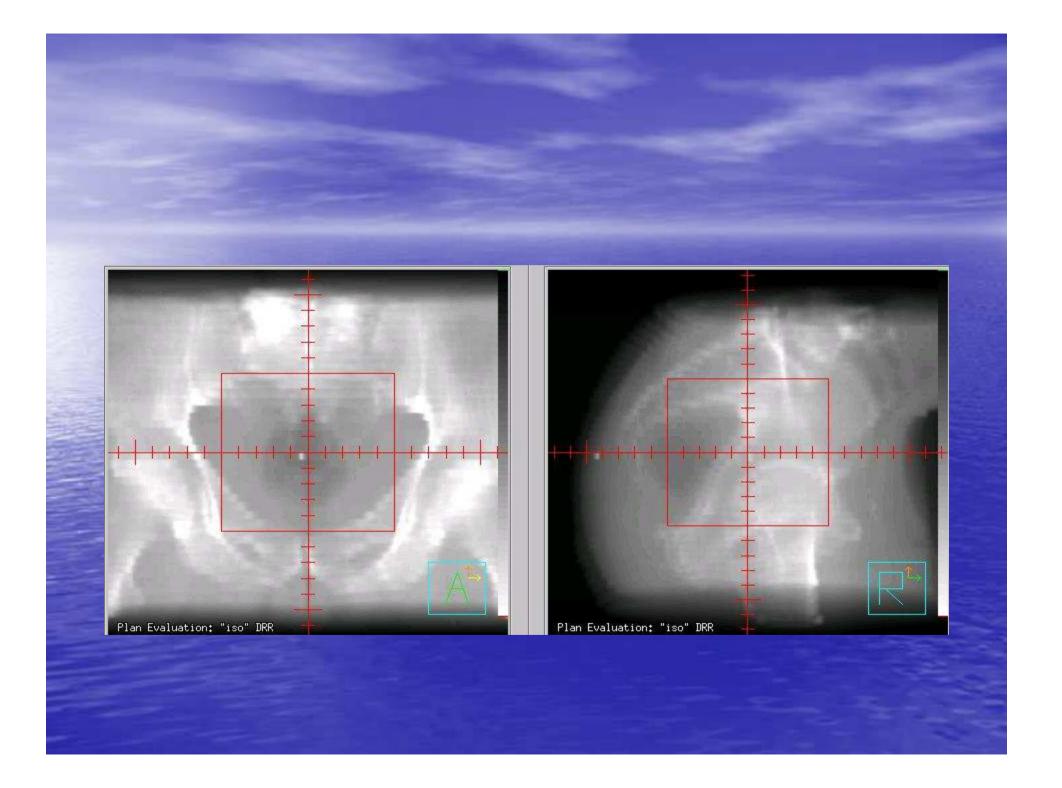


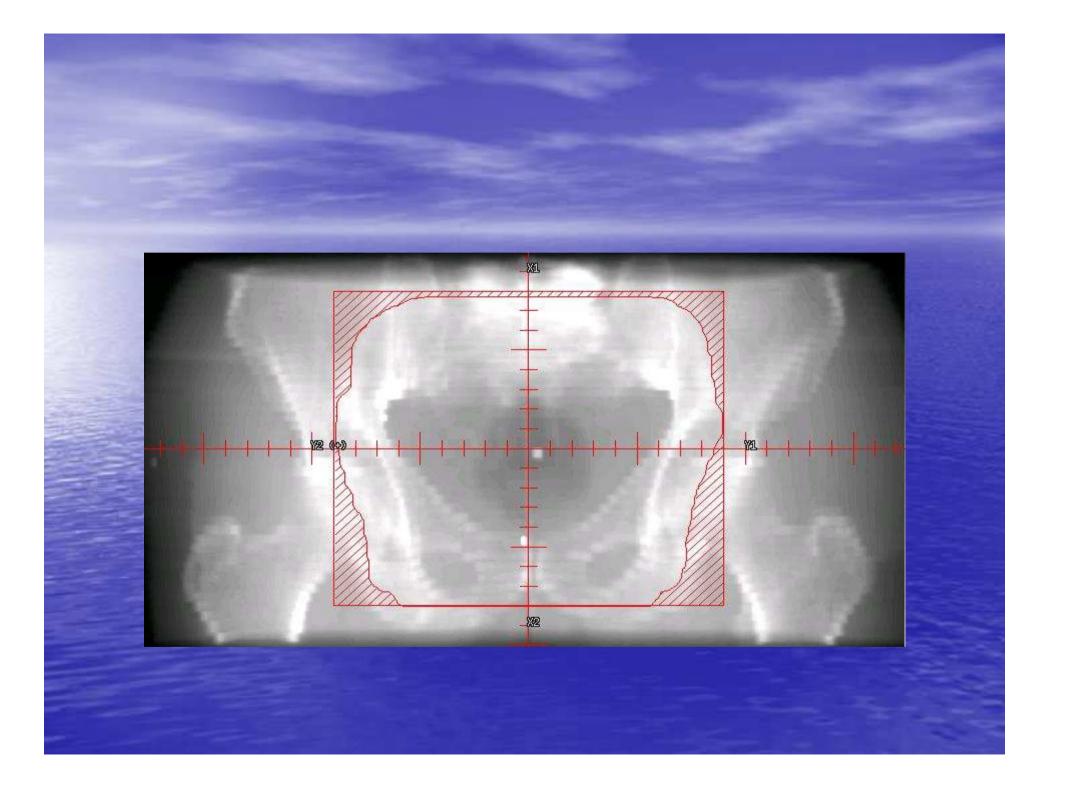


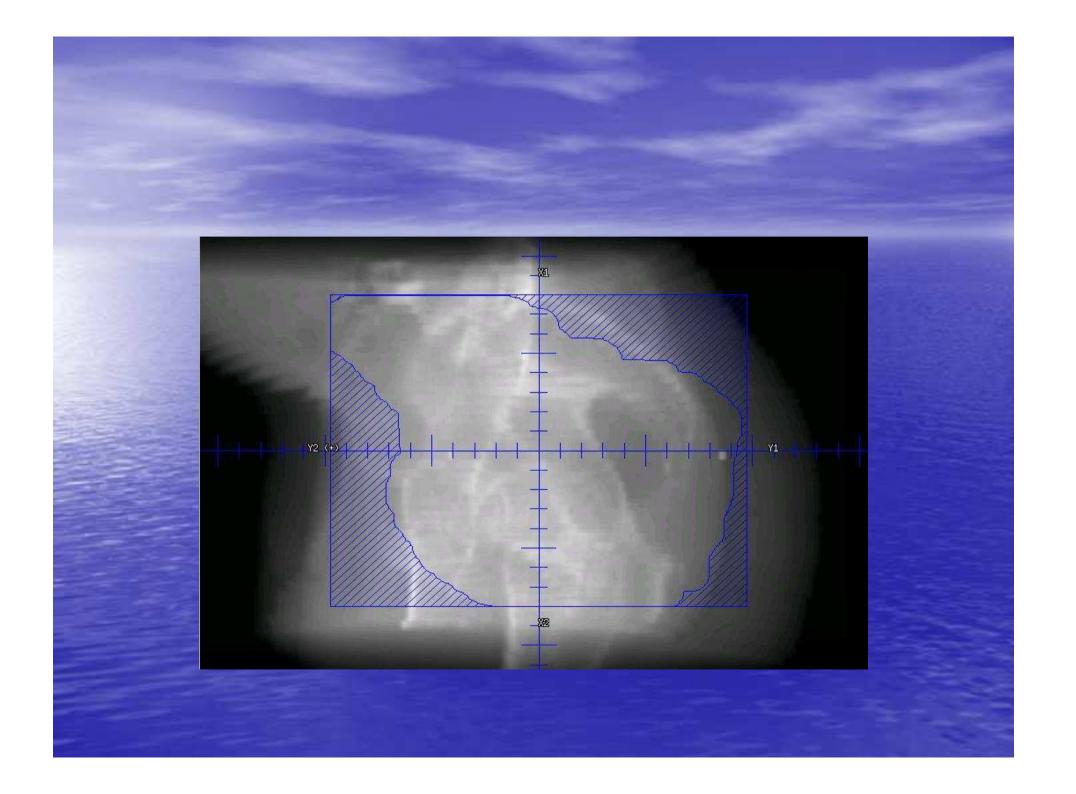


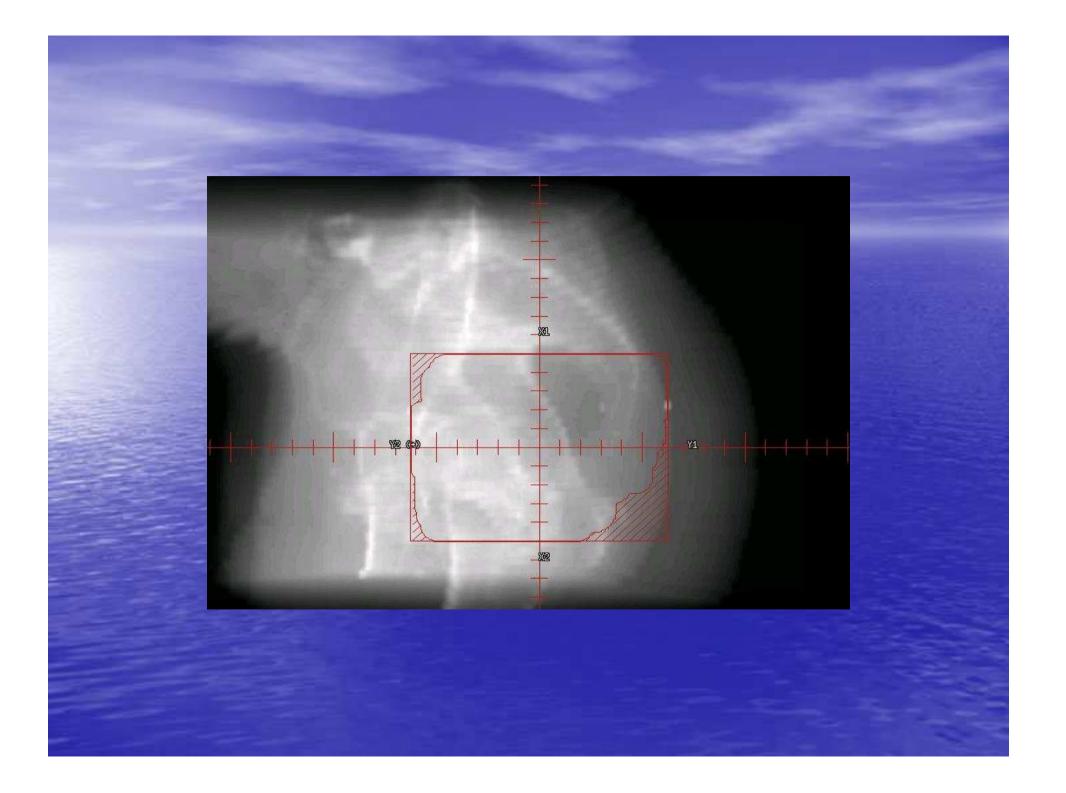


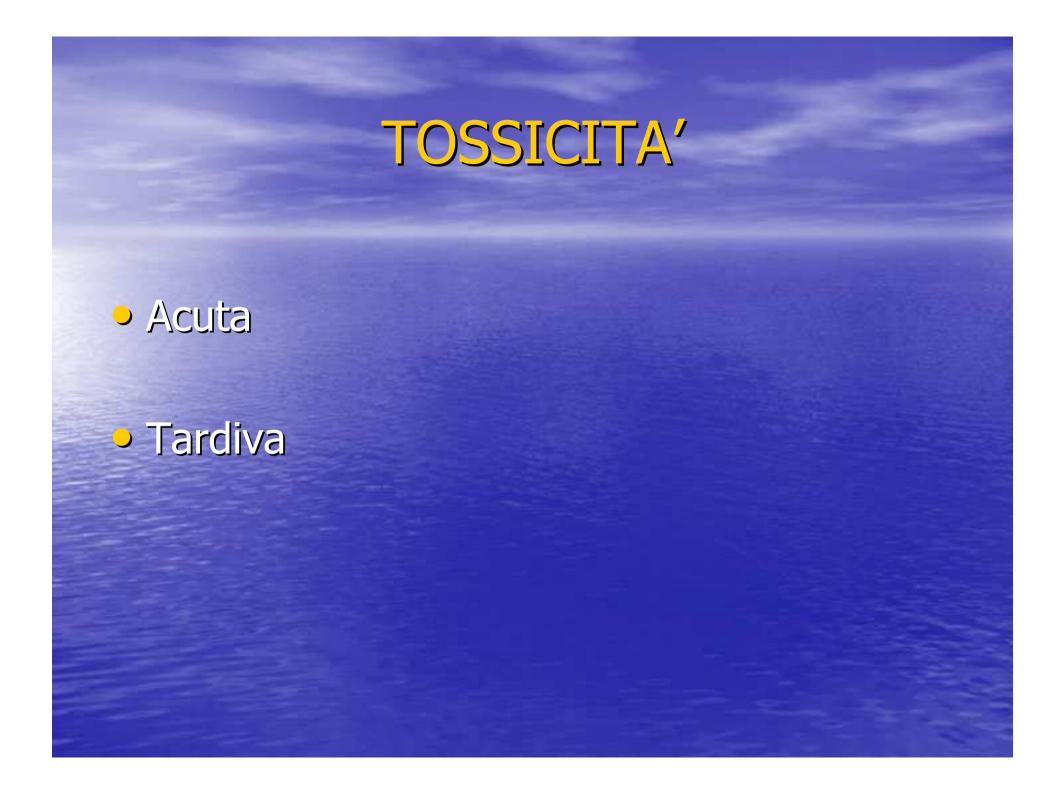












## COMPLICAZIONI DELLA RADIOTERAPIA

### **Acute**

Diarrea

Dolore addominale crampiforme

Proctite-tenesmo

Disuria

<u>Tardive</u> (>6 m. post-RT)

- Diarrea
- -Proctite
- -Sintomatologia ostruttiva tenue
- -Incontinenza (?)