

XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023

PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

Il paziente anziano: personalizzazione del trattamento - retto

Luciana Caravatta

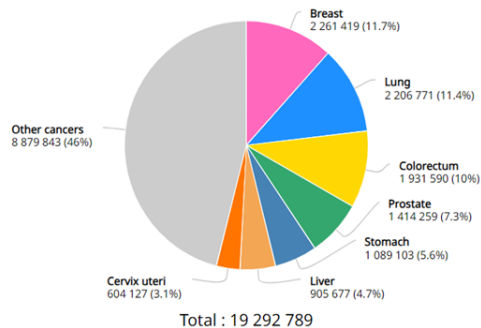
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Associazione Italiana
Radioterapia e Oncologia clinica

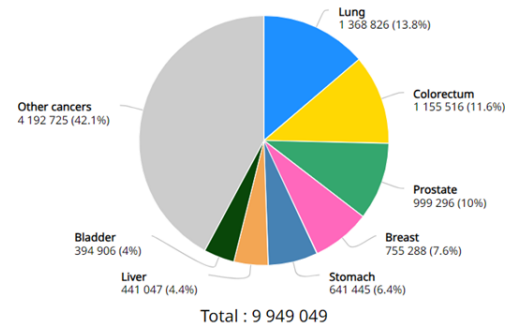
Estimated number of new cases in 2020, World, both sexes, all ages



Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
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Cancer Today - IARC, 150 Cours Albert Thomas, 69372 Lyon CEDEX 08, France - Tel: +33 (0)4 72 73 84 85 - powered by GLOBOCAN 2020

Estimated number of new cases in 2020, World, both sexes, ages 65+



Data source: GLOBOCAN 2020
Graph production: Global Cancer Observatory (<http://gco.iarc.fr/>)
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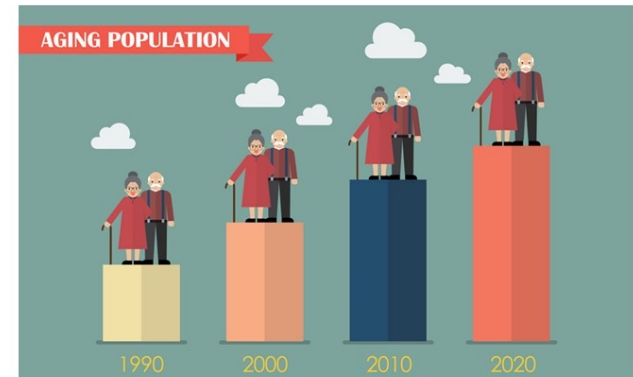
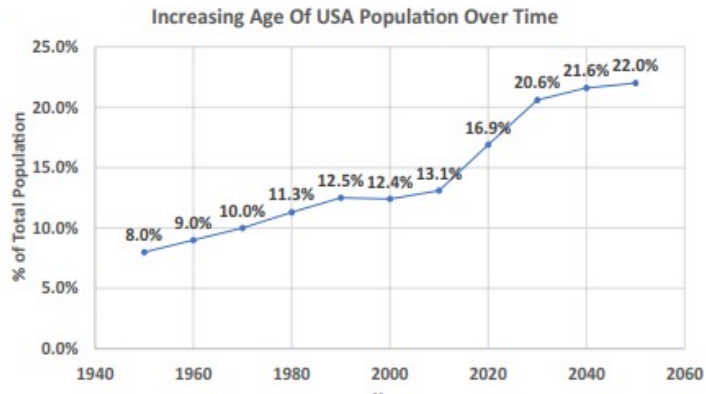
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over 50% of rectal cancer patients are older than 70 years

mean age at the time of diagnosis of 68 years for men and 72 years for women

- Although rectal cancer is **predominantly a disease of older patients**, **current guidelines do not incorporate optimal treatment recommendations for the elderly** and address only partially the associated specific challenges encountered in this population.
- **Can be adopted for the older patients the current recommendations on treatment strategies for the general population, with the same beneficial oncological and functional outcomes?**

Increase in the percent of adults >65 years old in the US population over time

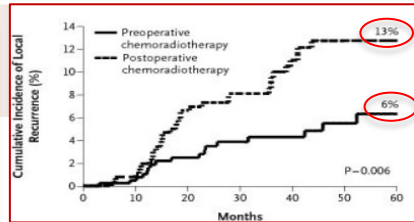


SEER Cancer Stat Facts: Colorectal Cancer. National Cancer Institute. Bethesda, MD, <https://seer.cancer.gov/statfacts/html/colorect.html>. Accessed 9/10/2022.

**“The Holy Plane”
TME surgery:**

- Reduction of CRM+ rate and LR rate = 30%-50%
- OS improvement up to 80%

**The Dutch TME Trial:
Preoperative RT+TME
vs. TME improves local
recurrence**



Radioterapia Oncologica:
l'evoluzione al servizio dei pazienti



**The German
CAO/ARO/AIO Trial:
Preoperative RT+TME
vs. postop RT
improves LC, compliance to
treatment and toxicity**



1980's

1990's

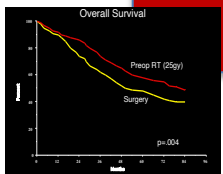
2000's

2010's

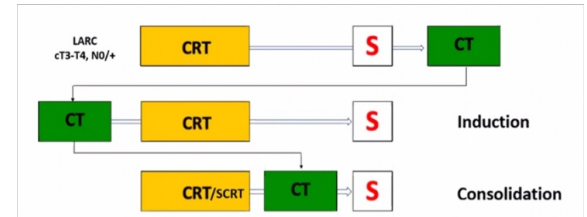
2020's

**The Swedish Trial:
Preoperative RT
improves
5y LC & OS**

**The British Trial:
Preoperative RT+TME vs. TME +selective CRT
improves LC
FFCD 9203, EORTC 22921:
Preoperative CCRT vs preoperative RT
improves LC and sphincter saving surgery**



Total Neoadjuvant Therapy



RISK-ADAPTED TREATMENT

	EARLY	INTERMEDIATE	LOCALLY ADVANCED	ADVANCED
MRI Risk group	cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), MRF-, no EMVI	cT2 very low, cT3 MRF- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI -	cT3b and/or EMVI+, and/or extranodal cN1-2 All with clear MRF and levators	cT3 MRF+, cT4 a,b, lateral node+
ESMO/ NCCN GL	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CTa. (CRT with evaluation, if cCR, wait-and-see, organ preservation)	Surgery (TME) alone or Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high-risk patients for surgery)	Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high-risk patients for surgery)	Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT. TNT approaches.

Limits of evidence-based data in older patients:

- unplanned subset analyses based on age and/or not originally stratified by age
- therefore, data, particularly overall survival data, may not be statistically valid based on the initial trial design and statistical plan
- then, they need to be interpreted with some caution.

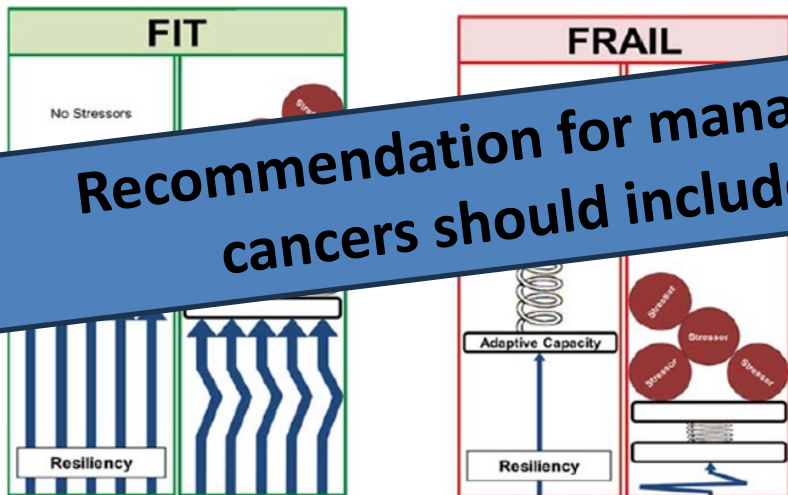
- The older patients are a **heterogeneous group** for which the chronological **age** and the **PS alone** may not carefully reflect their **functional or reserve state**.
- Determine which elderly patients **are suitable and can benefit** from healing therapies is essential to **optimize clinical results** while maintaining one **acceptable Quality of life**.

Dina Ioffe & Efrat Dotan. Current Treatment Options in Oncology (2023)

*The identification **frailty** could offer a personalized treatment approach, thanks to a multidisciplinary management of patients with increased risk of adverse outcomes.*

Recommendation for managing older patients with rectal cancers should include geriatric screening tools

... treatment toxicity because of age-associated conditions such as functional losses, cognitive impairment, or physiologic changes



Hurria A, et al. by U13 conference recommendations. J Clin Oncol. 2014

SYSTEMATIC COMPREHENSIVE GERIATRIC ASSESSMENT (CGA) IN ELDERLY PATIENTS WITH CANCER

Parameter assessed	Elements of the assessment
Functional status	Performance status
Autonomy assessment	ADL IADL
Comorbidity	The e Cumulative Illness Rating Scale for Geriatrics (CIRS-G)
Socioeconomic conditions	Presence and adequacy of a caregiver
Cognitive function	Folstein's Mini-Mental Status
Mobility	Get Up and Go
Emotional status	Geriatric Depression Scale-15
Pharmacy	Number of medications (≤ 3 or >3)
Nutritional status	Mini-Nutritional Assessment
Self-perception of health	G8 scale
IADL, instrumental activities of daily living; ADL, activities of daily living.	

MULTIDIMENSIONAL GERIATRIC ASSESSMENT	
DOMAINS	Test Score
COGNITIVE	
MMSE (minimal state examination)	24-30 normal cognitive status <24 cognitive deficit
GDS (geriatric depression scale)	10 - 15 severe depression 5 - 10 mild depression 0 - 5 absence of depression
FUNCTIONAL	
ADL (Activity of daily living)	0 - 6 (6 = absence of deficit)
IADL (Instrumental activity of daily living)	0 - 8 (8 = absence of deficit)
Tinetti assessment tool (gait and balance test)	0 - 1 not walking subject 2 - 19 high risk for falls 20 - 28 low risk for falls
NUTRITIONAL	
MNA - short (mini nutritional assessment)	12-14 good nutritional state 8 - 11 risk for malnutrition 0 - 7 malnutrition
DEFINITIVE SCORES for FRAILTY PHENOTYPE ASSESMENT	
Handgrip	no frailty intermediate or pre-frail frail
Gait speed	
CESD (center for epidemiologic studies depression scale)A-B	
Minnesota leisure activity	
Weight loss	

Hathout et al. J Gastrointest Oncol 2018

Class	Health status evaluation parameter	Tool	Therapeutic indications
Class 1: fit patient			Same as younger patients
Class 2: vulnerable patients			Adapted or attenuated treatment
Class 3: frail patient			Only supportive care and palliation

CGA-guided care is currently recommended by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) for the management of older patients with cancer.

*, age ≥85 years does not contraindicate treatment a priori, but extreme caution is required; †, Geriatric syndromes: delirium, dementia, depression, falls, neglect and abuse, spontaneous bone fractures. CIRS-G, Cumulative Illness Rating Scale's geriatric variant; IADL, instrumental activities of daily living; ADL, activities of daily living; MGA, multidimensional geriatric assessment.

Modified by Hathout et al. J Gastrointest Oncol 2018

AIRO2023

TUMORI DELL'ANZIANO

LINEE GUIDA
2019



Q DIFFUSIONE DELLE BUONE PRATICHE
Q CULTURA DELLA QUALITÀ
Q SICUREZZA DELLE CURE

Quality & Safety Day

19 DICEMBRE 2019

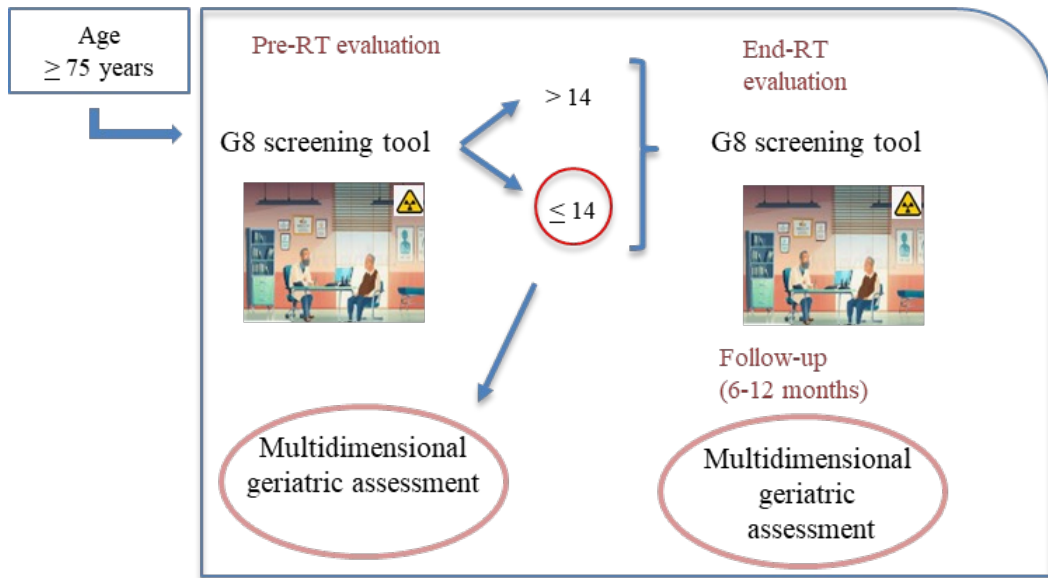
Qualità Globale delle evidenze	Raccomandazione	Forza della raccomandazione clinica
MODERATA	Nel paziente anziano con cancro il test di screening G8 dovrebbe essere preso in considerazione per diagnosticare la vulnerabilità.	Positiva forte

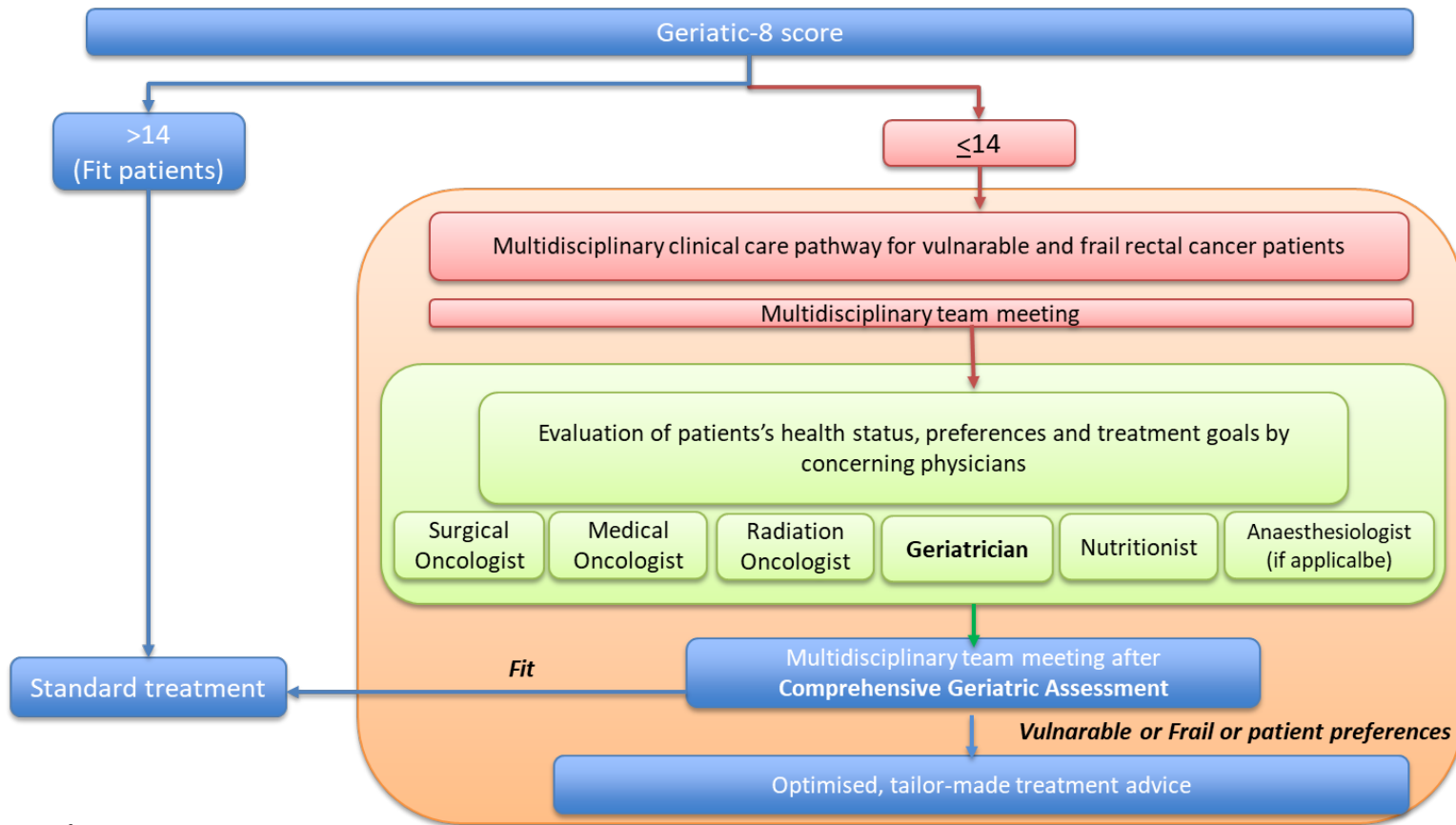
*Opinione espressa dal panel

Valutazione Multidisciplinare del paziente Oncologico Geriatrico (età ≥ 75 anni) con indicazione a trattamento Radioterapico a finalità curativa

L. Caravatta¹, M. Taraborrelli¹, L. A. Ursini¹, A. Di Pillo¹, L. Gasparini¹, I. Bottonne², M. Candolaro², E. Valeriani³, M. Di Nisio³, E. Parreco³, C. Natali³, D. Genovesi¹
1. UOC Radioterapia Oncologica, PO "S.S. Annunziata" Chieti 2. UOC Medicina Generale 2, PO "S.S. Annunziata" Chieti 3. Clinica Oncologica, PO "S.S. Annunziata" Chieti

G8 Screening tool			
Un punteggio totale ≤ 14 individua il paziente vulnerabile			
	Items	Possible answers	Score
A	L'apporto alimentare è diminuito negli ultimi tre mesi?	0: perdita di appetito grave 1: perdita di appetito moderata 2: nessuna perdita di appetito
B	Perdita di peso negli ultimi 3 mesi?	0: perdita di peso superiore a 3 Kg 1: non lo sa 2: perdita di peso tra 1 e 3 kg 3: nessuna perdita di peso
C	Mobilità	0: costretto a letto o su una sedia 1: capace ad alzarsi dal letto/sedia ma non di uscire 2: capace di uscire
E	Problemi neuropsicologici	0: demenza o depressione grave 1: demenza lieve 2: nessun problema psicologico
F	Body Mass Index (weight in kg/height in m2)	0: BMI BMI < 19 1: BMI 19 ≥ BMI < 21 2: BMI 21 ≥ BMI < 23 3: BMI BMI ≥ 23
H	Prende più di tre medicine al giorno?	0: sì 1: no
P	In generale, in confronto ad altre persone della Sua età, come considera il suo stato di salute?	0: cattivo 0,5: non lo sa 1: discreto 2: buono
	Età	0: >85 1: 80-85 2: <80
	Punteggio totale (0-17)	





Modified by Ketelaers, S.H.J. Cancers 2022

Optimised, Tailor-made Treatment Advice

Multidisciplinary management of elderly patients with rectal cancer: recommendations from the SICG (Italian Society of Geriatric Surgery), SIFIPAC (Italian Society of Surgical Pathophysiology), SICE (Italian Society of Endoscopic Surgery and new technologies), and the WSES (World Society of Emergency Surgery) International Consensus Project.

- *epidemiology,*
- *pre-intervention strategies,*
- *diagnosis and staging,*
- *neoadjuvant chemoradiation,*
- *surgery,*
- *watch and wait strategy,*
- *adjuvant chemotherapy,*
- *synchronous liver metastases,*
- *emergency presentation*

Podda et al. World Journal of Surgery (2021)

Frailty, but not age, is an **independent risk factor** for mortality, morbidity, and readmissions after rectal cancer surgery, radiotherapy, and palliative chemotherapy for metastatic disease.

Pre-intervention strategies: Frailty assessment and multidisciplinary evaluation.

Study	Phase + eligibility	Number of patients	Elderly-specific endpoints	Final recommendations
Boakye D, et al. Cancer Treat Rev. 2018	<p>Systematic review and meta-analysis</p> <p>37 cohort studies, (35 were on comorbidity and 2 on frailty)</p> <p>Severe comorbidity as ASA grade \geqIII or Charlson Comorbidity Index (CCI) \geq3 and mild/moderate comorbidity as CCI 1-2.</p>	<p>194,031</p> <p>Colorectal cancer patients</p>	<p>Colorectal cancer patients with mild/ moderate and severe comorbidity compared to patients without comorbidity showed a higher risk of:</p> <ul style="list-style-type: none"> • 30-day mortality (OR = 1.71 and OR = 2.62), • overall mortality (HR = 1.41 and HR = 2.03), • cancer-specific mortality (HR = 1.06 and HR = 1.14) <p>Frail patients showed higher overall mortality than non-frail patients (HR_{range}: 2.60-3.39).</p>	<p>Comprehensive geriatric assessment might help to optimize care of CRC patients, by improving early identification and management of comorbidities and geriatric syndromes.</p>

The use of a frailty score in the preoperative evaluation of rectal cancer patients above 70 years of age. (Weak recommendation, Low quality of evidence—2C). Agreement: 97.1%

Boakye D. Cancer Treatment Reviews (2018); Podda et al. World Journal of Surgery (2021)

GERICO trial: the effect of geriatric intervention in frail older patients receiving chemotherapy for colorectal cancer

- Randomised Phase 3 trial: **142 patients ≥70 years, III -IV stage**, receiving adjuvant or first-line palliative chemotherapy for CRC
- **Vulnerable patients (G8 questionnaire ≤14 points)** were randomised 1:1 to Comprehensive geriatric assessment (**CGA**)-based interventions or standard care.
- Primary outcome = chemotherapy completion without dose reductions or delays.
- Secondary outcomes = toxicity, survival and QoL

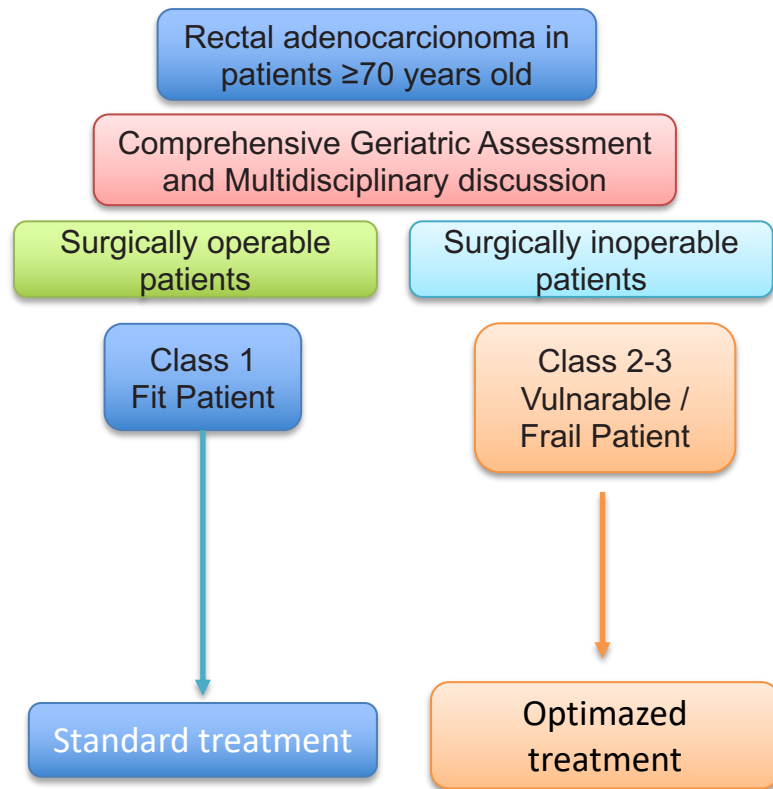
Interventions: medication changes (62%), nutritional therapy (51%) and physiotherapy (39%).

Completed scheduled chemotherapy = 45% of Interventional patients vs. 28% of control, $P = 0.0366$).

Severe toxicity: 28% of interventional patients vs 39% of controls ($P = 0.156$).

QoL improved in interventional patients compared with controls with the decreased burden of illness ($P = 0.048$) and improved mobility ($P = 0.008$).

C. M. Lund. Journal of Cancer (2021)



Treatment strategies:
Neoadjuvant CRT?
Surgery?
Adjuvant chemotherapy?

Treatment strategies: Indication, timing, compliance, and outcomes of Neoadjuvant CRT and surgical TME, followed by adjuvant chemotherapy.

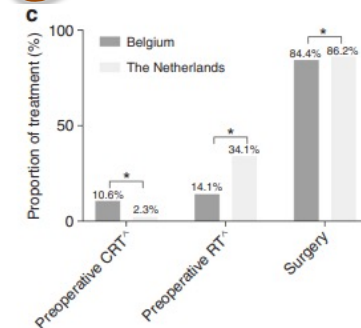
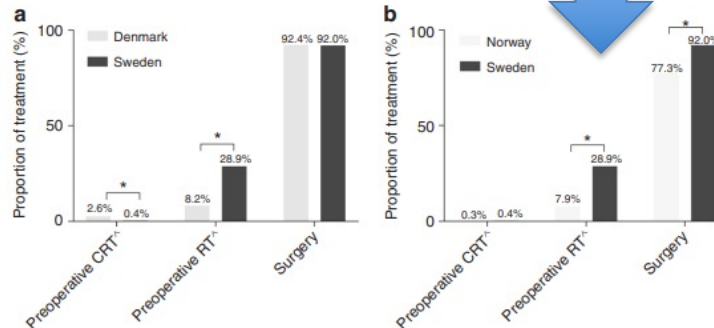
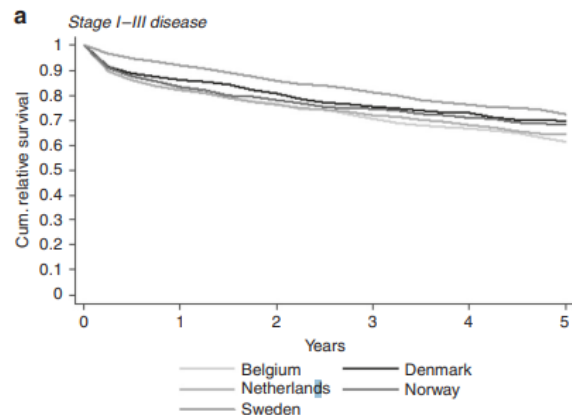
- Patients aged ≥ 70 years had a **higher risk** of treatment-related AEs and inferior Survival compared to younger patients treated with Neoadjuvant CRT and surgical TME, followed by adjuvant chemotherapy.
- Several studies demonstrated that **older patients** with LARC were **less likely to receive standard therapy** with **lower rates** of **surgical interventions** and **CHT use**

Shahir MA. Eur J Cancer. 2006; Babaei M, et al. Clin Colorectal Cancer. 2018

Treatment and survival of rectal cancer patients over the age of 80 years: a EURECCA international comparison

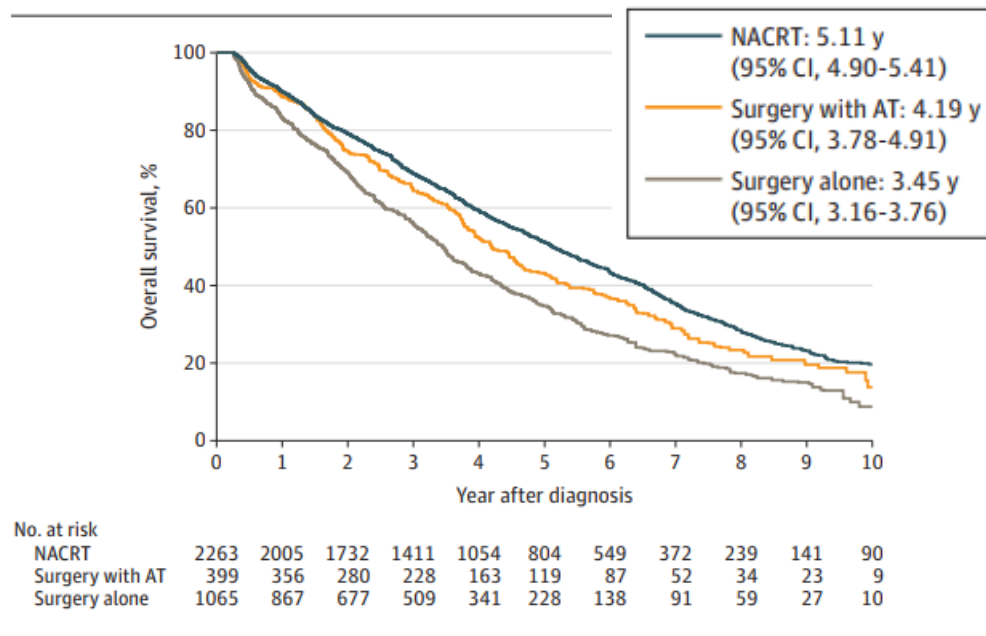
19 634 rectal cancer patients

5-year relative survival varied from 61.7% in Belgium to 72.3% in Sweden



YHM Classen et al. British Journal of Cancer. 2018

- ❑ Cohort study on **3868 patients (80 years and older)** with LARC who underwent surgical resection in the 2004-2016 National Cancer Database by the American College of Surgeons and the American Cancer Society
- ❑ Approximately **40% of older patients with LARC did not receive the current standard of care**, with more than 30% of patients receiving a surgery-alone approach.
- ❑ The utilization of NACRT gradually increased over the study period. The greatest rise was seen from 2011 to 2012; 207 patients (49.8%) received NACRT in 2011, with an increase to 229 (58.3%) in 2012.



Patients who had received NACRT had a **significantly greater** likelihood of having an R0 resection (OR, 2.16; 95% CI, 1.62-2.88)

Table 1. Tumor and patients' characteristics (n= 116)

Age (yr), mean (range)	75.8(70-88)		
	N (%)		N (%)
Gender		Type of surgery	
Male	79(64.8)	AR	75(64.7)
Female	37(31.6)	TEM	4(3.5)
		APR	23(19.8)
		No Surgery	14(12)
ECOG PS		Margin status	
0-1	103(88.8)	R0	99(85.3)
2	13(11.2)	R1	3(2.5)
		No Surgery	14(12.2)
Comorbidity		TRG	
Cardiovascular disorders	56(48.2)	1	28(27.5)
Diabetes	10(8.6)	2	17(16.7)
Any	30(26)	3	35(34.4)
missing	20(17.2)	4	18(17.6)
		5	2(1.9)
		missing	2(1.9)
Clinical Stage		Pathological stage	
cT3N0	31(26.7)	T	
cT3N+	66(56.9)	T0	25(24.5)
>cT3N+	19(16.4)	T1	8(7.8)
		T2	31(30.4)
		T3	36(35.4)
		T4	0(0)
		missing	2(1.9)
		N	
Radioterapy total dose (cGy)		Chemotherapy schedule	
≤5040	72(62.1)	N0	83(81.5)
>5040	44(37.9)	N1	15(14.7)
		N2	2(1.9)
		missing	2(1.9)

Plafur: Cisplatin and 5-FU; Xelox: Capecitabine and Oxaliplatin; AR: anterior resection; TEM: transanal endoscopic microsurgery; APR: abdominoperineal resection; R1: tumor cells into resection margin; TRG: tumor resection grade.

Table 2. Acute Toxicities

Acute Toxicities (116 pts)	G0	G1	G2	G3
Skin Toxicity	62 (53.4%)	22 (19.0%)	31 (26.7%)	1 (0.9%)
GI Toxicity	37 (31.9%)	38 (32.8%)	39 (33.6%)	2 (1.7%)
GU Toxicity	87 (75.0%)	26 (22.4%)	3 (2.6%)	0 (0%)
Hematologic Toxicity	93 (80.2%)	10 (8.6%)	10 (8.6%)	3 (2.6%)
MSKCC (58 pts)	Excellent	Good	Fair	Poor
	36 (62%)	5 (8.6%)	6 (10.4%)	11(19%)

Neoadjuvant chemoradiotherapy in older rectal patients with cancer: Tolerability and sphincter functionality
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Table 3. Studies evaluating outcomes and toxicities in elderly rectal cancer patients.

Author years	Study Design	N°	Age	Treatment	Permanent stoma	R0	pCR	OS	DFS	Toxicities ≥G3	
										Acute	Late
Tougeron 2012	R	125	>70	nLCRT + S	36%	90%	41% T downstaging	84% (2 yr) 76% (3 yr)	NR	15%	NR
Francois 2014*	R ^Δ	142	≥70	nLCRT ^Δ +S	33%	88.6%	14.7% [#]	80.5% (3 yr)	NR	25.6%	NR
Jiang 2015*	R	295	>70	nLCRT + S	NR	78%	16%	76% (5 yr)	NR	NR	
Choi 2016*	R	56	>70	nLCRT + S	8.9%	97.8%	15.6% [#]	81.7% (3 yr) 67.5% (5 yr)	77.8% (3yr) 60.0% (5yr)	Diarrhea: 16.1% Neutropenia 1.8%	4.5%
Sung 2017*	R	310	≥70	nLCRT + S [†]	9.7%	NR	14.8%	79.5% (5 yr)	65.5% (5yr)	Hematologic: 16.1% Non-hematologic: 14.8%	2.6%
Rosa 2021	R	116	≥70	nLCRT + S	24.5%	85.3%	27.5%	86.5% (3 yr) 78.1% (5 yr)	82.8% (3yr) 73.3% (5yr)	5.2%	2.6%

Short-course radiotherapy compared to neoadjuvant long course chemo-radiotherapy

Author	Treatment	N° Studies / patients	pCR rate	sphincter preservation rate	grade 3-4 acute toxicities	grade 3-4 late toxicities	post-treatment complications	OS	DFS	LC	DM
Ma B. Clin Colorectal Cancer. 2018	SCRT vs LCRT	19 Studies 7191 patients	LCRT > SCRT OR = 0.05, P < 0.01 *	OR = 1.62, P = 0.25	SCRT < LCRT OR = 0.09, P < 0.01	OR = 1.02, P = 0.96	OR = 1.19, P = 0.30	HR = 0.88, P = 0.34	HR = 0.72, P = 0.14	HR = 0.75, P = 0.21	HR = 0.97, P = 0.84
Wang X. Plos One. 2018	Long term outcomes SCRT vs LCRT	11 studies 1984 patients						HR = 0.92, P = 0.44	HR = 0.94, P = 0.50	OR = 0.73, P = 0.11	
Zhou ZR. Surg Onc 2014	SCRT Immediate S vs LCRT Delayed S	12 studies 2187 patients	LCRT > SCRT RR = 0.15, P = 0.003	RR = 1.00, P = 0.92	LCRT > SCRT RR = 0.13, P < 0.00001	RR = 1.30, P = 0.55		RR = 0.89, P = 0.21	RR = 0.93, P = 0.42	RR = 0.83, P = 0.29	RR = 0.95, P = 0.63
Qiao Li W. Int J Colorectal Dis. 2019	SCRT Delayed S vs LCRT	7 studies 4973 patients	RR = 0.74, P = 0.39 §		RR = 0.78, P = 0.68 §		RR = 1.21, P = 0.16	HR = 1.30, P = 0.52 §	HR = 1.10, P = 0.64	RR = 1.27, P = 0.70	RR = 1.06, P = 0.58
Yu Y. Rev Esp Enferm Dig. 2019	SCRT (w/wt CHT) vs LCRT	16 studies 2773 patients	RR = 0.54, P < 0.05 °			RR = 1.10, P = 0.01				RR = 0.55, P = 0.27	RR = 1.03, P = 0.22

*but **delayed surgery** or **adding consolidation chemotherapy** might be **improved pCR**; § subgroup analysis revealed that **SCRT without adjuvant chemotherapy** resulted in **lower** treatment-related grade 3-4 toxicity than PLCRT (RR = 0.19, P < 0.01), but also resulted in **significantly lower overall survival** (HR = 2.05, P = 0.02) and pCR (RR = 1.37, P = 0.14);

° subgroup analysis, **LCRT better pCR and tumor downstaging rate** compared with SCRT in the RCT subgroup. Besides, LCRT also presented a better pCR rate **compared with SCRT without CHT**

Health-related quality of life outcomes after SRT or LCRT based on EORTC QLQ-C30 questionnaire

EORTC QLQ-C30 subscales	TROG 01.04 trial			Polish trial			Wiltink et al		
	SCRT	LCRT	P value	SCRT	LCRT	P value	SCRT	LCRT	P value
Patients	143	154		111	110		306	85	
Function									
Physical	78.0	79.9	0.26	76	75	0.78	82.6	84.5	0.56
Role	63.9	68.2	0.26	74	73	0.76	83.3	82.5	0.73
Emotional	NR	NR	NR	66	67	0.69	86.3	86.9	0.85
Cognitive	NR	NR	NR	77	76	0.72	84.1	84.0	0.90
Social	68.5	68.9	0.31	75	73	0.58	87.7	84.6	0.27
Global	61.1	61.8	0.44	57	61	0.22	78.9	79.6	0.90
Symptoms									
Fatigue	36.4	35.5	0.62	34	36	0.67	22.5	23.8	0.59
Nausea/vomiting	NR	NR	NR	8	5	0.03	1.3	5.9	< 0.01
Pain	23.0	22.0	0.98	28	31	0.73	11.1	11.2	0.92
Dyspnoea	NR	NR	NR	18	18	0.64	11.6	11.8	0.89
Insomnia	NR	NR	NR	36	34	0.62	18.5	15.4	0.42
Appetite	20.6	17.3	0.37	13	14	0.88	4.6	8.5	0.12
Constipation	NR	NR	NR	23	19	0.34	10.8	8.6	0.51
Diarrhoea	NR	NR	NR	23	18	0.19	10.6	5.8	0.09
Financial	NR	NR	NR	33	38	0.20	6.8	9.5	0.27

A higher score for functioning reflects better functioning, whereas a higher score for symptoms represents a higher level of symptoms and decreased health-related quality of life. EORTC: European Organization for Research and Treatment of Cancer; PSRT: preoperative short-course radiotherapy; PLCRT: preoperative long-course chemoradiotherapy; NR: not reported.

Ma B. Clin Colorectal Cancer. 2018

short-course radiotherapy compared to neoadjuvant long course chemo-radiotherapy

Study	Phase + eligibility	Treatment	Median PFS, OS months (HR [CI 95%])	Elderly-specific endpoints	Final recommendations
Francois E. J Clin Oncol 2021	Phase III PRODIGE 42/GERICO 12 NACRE (preliminary) Patients ≥75 years old, PS 0–2 cT3 or cT4 (or very low cT2), M0 rectal adenocarcinoma, <12 cm from the anal verge	A: Neoadjuvant CRT (50 Gy, 25 fx +capecitabine), delayed surgery B: Short-course RT (25 Gy, 5 fx), delayed surgery	Surgery performed: 92% (arm A); 96% (arm B) No difference in R0 resection rate Better OS in SCRT arm (p=0.04) and trend in favor SCRT arm for specific survival (p=0.06)	maintenance of autonomy according to the IADL (instrumental activities of daily living) score - pending	Short-course radiotherapy with delayed surgery is associated with better compliance than CRT followed by delayed surgery (0% vs 14% did not receive planned treatment)
Francois E. European Journal of Cancer 2023	Phase III, PRODIGE 42/GERICO 12 NACRE (closed due to poor accrual) 101 patients, Median age: 80 years (75–91)	A: Neoadjuvant CRT (50 Gy, 25 fx +capecitabine), delayed surgery B: Short-course RT (25 Gy, 5 fx), delayed surgery	R0 resection rate (first co-primary objective): A- 88%; B- 84.3% (non-inferiority p=0.28) No significant difference in terms of operative technique (p = 0.57). Better OS in SCRT arm (HR 0.28, P=0.05) and specific survival (HR 0.21, p= 0.027) No differences in Recurrence free survival and Local recurrence free survival	IADL score not different during the pre-operative phase and between baseline and M12; 3 months post-operative: arm A- 44.8%, arm B - 14.8%; p = 0.032	Although the main objectives of the study were not achieved, SCRT followed by delayed surgery could represent a preferred treatment option in patients ≥75 years with locally advanced rectal cancer

Short-course radiotherapy with delayed surgery in elderly frail patients with locally advanced stage II–III resectable rectal cancer. (*Weak recommendation, Moderate quality of evidence—2B*). Agreement: **87.9%**

Adjuvant Chemotherapy

Study	Phase + eligibility	N patients	Age	Treatment	Results
Lund JL J Geriatr Oncol 2016	SEER Medicare yp stage 0-III rectal	1316	>66 years (up to more than 80 years)	CRT or RT and resection Post-op 5Fu/Cape Or 5Fu+Ox	The benefit of postoperative 5-FU/capecitabine over observation was restricted to patients aged 66-74 years (aHR=0.46, 95%CI: 0.30, 0.72) with an absolute risk reduction in all-cause mortality of 14% at 3 years (aRD=-0.14, 95%CI: -0.23, -0.04) and 23 % at 5 years (aRD=-0.23, 95%CI: -0.33, -0.12). Patients aged 75+ (aHR=1.11, 95%CI: 0.76)
Huang XZ Oncotarget 2016	SEER Medicare yp stage 1-III rectal	763	>66y ears	CRT or RT and resection Post-op 5Fu/Cape Or 5Fu+Ox	Oxaliplatin in elderly patients showed higher incidence of acute renal failure compared with younger patients ($\Delta\% = 7.27\%$, $p = 0.010$) ypN+ : Oxaliplatin significantly improved OS in patients younger than 73 years (HR = 0.411, $p = 0.009$), but not in those aged ≥ 73 years (HR = 1.229, $p = 0.501$), compared with the 5-Fu group.
S.L. Liu Curr Oncol. 2018	Retrospective study stage II/III rectal cancer	286	152 pts = 65-69 years 92 pts = ≥ 70 years (range: 31-92 years)	Surgery (with or without nadj C-RT) Only 27 patients (n = 29%) of 70 years of age and older received adj	The rate of adj CT omission was significantly higher in patients ≥ 70 years than in younger patients ($p < 0.001$). In patients ≥ 70 years, grade ≥ 1 CHT-related toxicities were significantly higher in patients treated with adj: 85% vs. 68% not treated with adj ($p < 0.05$). The rate of adj CHT completion was significantly lower in patients ≥ 70 years (52%) than in those less than 65 years (70%, $p < 0.01$) 5yOS (without adj) <65 years = 70.8%; 65-69 years = 58.8%; ≥ 70 years = 52.3% ($p < 0.05$) 5yOS (with adj) <65 years = 86.2%; 65-69 years = 90.2%; ≥ 70 years = 88.9% ($p < 0.05$)

Adjuvant Chemotherapy ...What have we learned from colon cancer studies?

NSAPB C-07	Oxaliplatin + 5-FU could improve DFS in patients > 70 years But possibly related to higher rates and grades of toxicities compared to younger patients
ACCENT	Oxaliplatin + 5-FU could improve DFS in patients aged 50–65 years, while patients aged ≥ 70 years experienced less benefit from the addition of oxaliplatin
SEER study	The addition of Oxaliplatin for stage III colon cancer in patients >75 years offered no more than a small incremental benefit compared to non oxaliplatin regimens

For **selected stage III and stage II high-risk elderly patients** with rectal cancer who **underwent radical surgery with curative intent**, a **fluoropyrimidine-based adjuvant** chemotherapy should be preferred to clinical and radiological follow up. Decision has to be taken after a multidimensional and geriatric assessment and must be shared within the multidisciplinary board, taking into account individual cancer risk of recurrence, DYPD evaluation, **previous treatment (surgery alone or preoperative chemo-radiotherapy)**, patient's performance status and comorbidities (*Weak recommendation, Low quality of evidence—2C*). **Agreement: 93.8%**

Mini-invasive Surgery

Although limited data specific to the elderly, **advantages of TEM approach for elderly patient with more comorbidities**: relative increased safety, faster operative time, decreased blood loss, shorter hospital-stay, and decrease in stoma formation.

Mini-invasive Surgery

Gilbert A. Lancet Health Longev. 2022

Study	Phase + eligibility	N patients	Age	Treatment	Results	Elderly-specific endpoints	Final recommendations
TREC trial Gilbert A., Lancet Health Longev. 2022	non-randomised registry cohort T1-2N0, unsuitable for TME (high risk of complications from TME on the basis of frailty, comorbidities, and older age)	61	median age 74 years (IQR 67–80)	SCRT (25 Gy , 5 fx) + transanal endoscopic microsurgery (TEM)	Organ preservation: 56/61 patients (92%) 3years Local Recurrence-Free Survival: 91% (95% CI 84–99)	Patient-reported benefits of organ preservation sustained over the 36-month follow-up with quality-of-life scores and physical and social functioning scores similar to those in their pre-treatment status.	Support use of organ preservation via SCRT and TEM as a leading option for patients with early rectal cancer who are unfit for radical surgery .

Consider elderly patients with **small cT2/T3 N0 low rectal cancers** suitable for neoadjuvant therapy and **organ sparing transanal local excision** (*Strong recommendation, Moderate quality of evidence—1B*). **Agreement: 91.2%**

Non-operative treatment strategy - Watch and wait

Haak Hester E. European Journal of Surgical Oncology 2020

Study	Phase + eligibility	N patients	Age	Treatment	Results	Elderly-specific endpoints	Final recommendations
Haak Hester E. (Dutch Watch-and-Wait Consortium) European Journal of Surgical Oncology 2020	National Network Register (prospective and retrospective) Patients aged ≥ 75 , T1-T4, N0-N+ and ≥ 2 years of follow-up with cCR after NAD LCRT or SCRT	43	median age 78 years (IQR 75 - 87)	W&W approach (minimum follow-up of two years)	3-year local regrowth-free rate: 88%, 3-year non-regrowth DFS: 91%, OS: 97% 3-year colostomy-free rate: 93%	Bowel- and urinary dysfunction scores at 3, 12 and 24 months indicated good continence, no or minor low anterior resection syndrome-score and moderate urinary problems (Vaizey incontinence score)	W&W for older patients with a clinical (near) complete response appears to be a safe alternative to TME , with a very high pelvic control rate, and few rectal cancer related deaths. Most patients can avoid major surgery and a definitive colostomy, and have a reasonable anorectal and urinary function.

Watch and wait strategy is suggested in selected frail elderly patients with low-rectal tumors in case of complete clinical response after neoadjuvant therapy. A stringent surveillance protocol, at least in the first 3 years, and a candid discussion with the patient about the potential risks of this strategy are recommended (*Weak recommendation, Low quality of evidence—2C*). **Agreement: 97.0%**

How to improve the clinical complete response probability?

Dose escalation?

Dose-response analyses indicate that doses of 72 Gy or higher are needed to achieve a major tumour response in 50 % of cT3–4 rectal tumours

Endoluminal high-dose rate (HDR) Ir-192

- local tumor response: 85%;
- 58% complete response and 27% partial response

Papillon popularized contact X-ray brachytherapy (CXB) 50 kVp

- 5 years- local control 60–70% in T2–T3 rectal tumor
- cCR above 70 % and up to 80% (T<3cm)

Comparison of CXB and HDR-BT: Technical considerations

E. Fokas. Cancer Treatment Reviews 2023

Summary of efficacy and toxicity (proctitis) data on EBRT in combination with endorectal brachytherapy for organ preservation in rectal cancer									
Study	TNM stage	n	Median age	EBRT	CXB	HDR--BT	cCR rate	Toxicity rate	Toxicity grade
Gerard 2004*	cT2-3	88	68 (28–82)	EBRT 13x3 Gy	35/30/20 Gy	–	26 %	<5%	Proctitis G3
Rijkmans 2017	cT2-3	38	83 (57–94)	EBRT 13 × 3 Gy	–	3 × 5–8 Gy	61 %	40 %	Proctitis G2-3
Appelt 2015	cT2-3	55	67 (8–75)	CRT 30 × 2 Gy	–	1x 5 Gy	78 %	7 %	Proctitis G3
Garant 2019	cT1-4	94	81 (60–97)	EBRT 16 × 2.5 Gy	–	3 × 10 Gy	86.2 %	19 %	Proctitis G3
Myint 2018	cT2-3	83	72 (36–87)	CRT 25 × 1.8 Gy	3 × 30 Gy	–	63.8 %	6 %	Proctitis G2 only
Myint 2017	cT1-4	200	74 (32–94)	CRT 25 × 1.8 Gy	3 × 30 Gy	–	72 %	11 %	Proctitis G2 only
Dhadda 2017	cT2-3	74	74 (39–93)	CRT 25 × 2 Gy	3 × 30 Gy	–	86 %	11 %	Proctitis G3

Abbreviations: EBRT, external beam radiotherapy; CRT, chemoradiotherapy (5-Fluorouracil- or capecitabine-based); CXB, contact brachytherapy; HDR-BT, high dose rate brachytherapy, cCR, clinical complete response

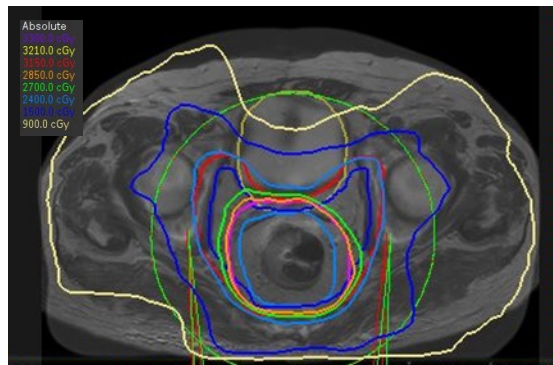
*In the LyonR96-02 trial, patients were randomized to either EBRT or EBRT plus CXB. The rates of sterilized specimen with few residual cells (57 % v 34 %; P = 0.027) as well as sphincter preservation (76 % v 44 %; P < 0.004) were higher in favor of the CXB group.

Tumor volume is the most important predictive factor for tumor response and a higher dose to the brachytherapy CTV increases the risk of severe clinically and endoscopically observed proctitis after definitive radiotherapy in elderly patients with rectal cancer.

RADIOTERAPIA PREOPERATORIA SHORT COURSE CON INTENSIFICAZIONE DI DOSE MEDIANTE VMAT- SIB E CHIRURGIA RITARDATA NEL CARCINOMA DEL RETTO: STUDIO DI FASE II (Short course Preoperative radiotherapy with dose intensification and delayed surgery in rectal cancer: the SPEEDY trial)

Vulnerable patients unfit for LCRT

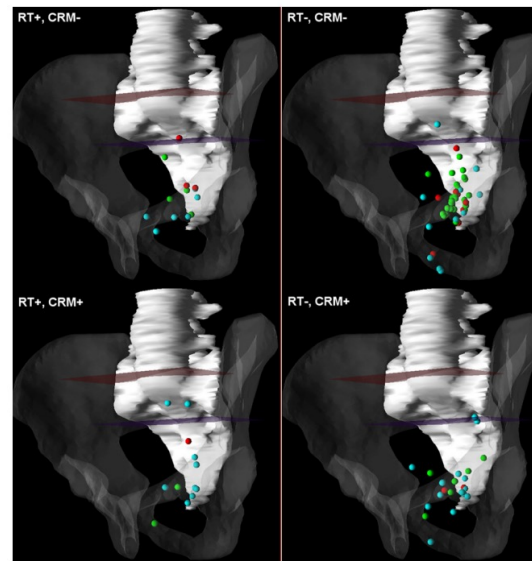
VMAT/SIB 25 Gy, 5 Fx – 30 Gy, 5 Fx
+ consolidative Cape + Surgery (8-12 w)



Clinical Target Volume modulation

Consider limitation of CTV:

- external iliac nodes for cT4 or extensive nodal disease
- upper CTV border to S2/S3 interspace for low or mid rectal cancers
- obturator nodes might be excluded in patients N0 and small tumour
- reduction margin of uninvolved mesorectal or presecral tissue in cranial-caudal direction



Nijkamp J Int J Radiat Oncol Biol Phys 2011

Conclusion 1

- Radiotherapy represents a key component of the management of older patients with rectal cancer
- Determine which elderly patients are suitable and can benefit from healing therapies is essential to optimize clinical results while maintaining one acceptable Quality of life.
- Management of older patients requires a sensitive and empathic multidisciplinary individualized approach with highly qualified and experienced members

Conclusion 2 - Fit patients (with acceptable sphincter tone)

- Consider indications for preoperative radio(chemo)therapy the same as for fit younger patients
- 5 × 5 Gy with at least 8 week interval to surgery could be offered as valid alternative in intermediate MRI risk group and LARC
- Consolidative short chemotherapy (5FU/Capecitabine) could be considered in the interval to surgery to improve clinical outcomes
- For patients with cT2 or cT3a/cT3b disease consider up-front radiotherapy with organ preservation intent (i.e. watch-and-wait for clinical complete response or full-thickness local excision for near clinical complete response/small residual tumour)

Conclusion 3 - Vulnerable patients and/or surgical risk

- Consider preoperative radio(chemo)therapy with limitation of CTV
- Consider **watch-and-wait strategy** in patients with clinical complete response also in those receiving **5 × 5 Gy**
- Consider **short chemotherapy consolidation or dose intensification** (contact X-ray or endoluminal high dose rate brachytherapy; EBRT boost for high- low rectal cancer)
- Consider diverting colostomy if necessary

Conclusion 4 - Frail patients

- For early/intermediate and medium size tumours consider radical radiotherapy (EBRT +/- boost or contact X-ray or endoluminal HDR-BT)
- For very frail patients consider 5x5 Gy to CTV that included only gross tumour with small margin

NEW HYPOTHETICAL SCENARIOS

- **Beyond standard outcomes:** i.e. efficacy in term of **active life expectancy** (numbers of years an individual lives independently without significant disability) instead of OS or DFS; **compliance to treatment ...**
- **Prioritization of patient-centered outcomes:** functional or health related quality of life (HRQOL) end-points

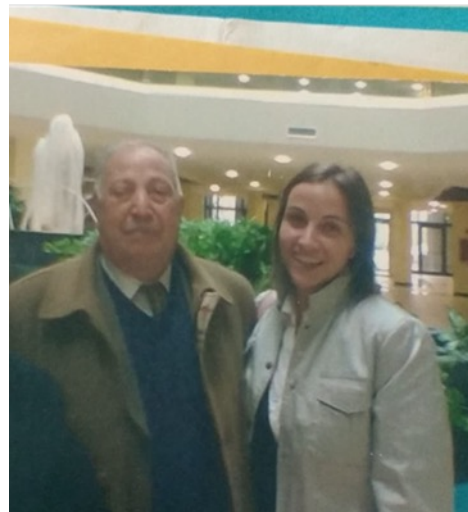
But currently ...

Multidisciplinary integration team and CGA-guided care is recommended!

Radioterapia Gemelli Molise 2006

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"In the middle of difficulty lies opportunity"
(Albert Einstein)

... and thank you for your attention

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