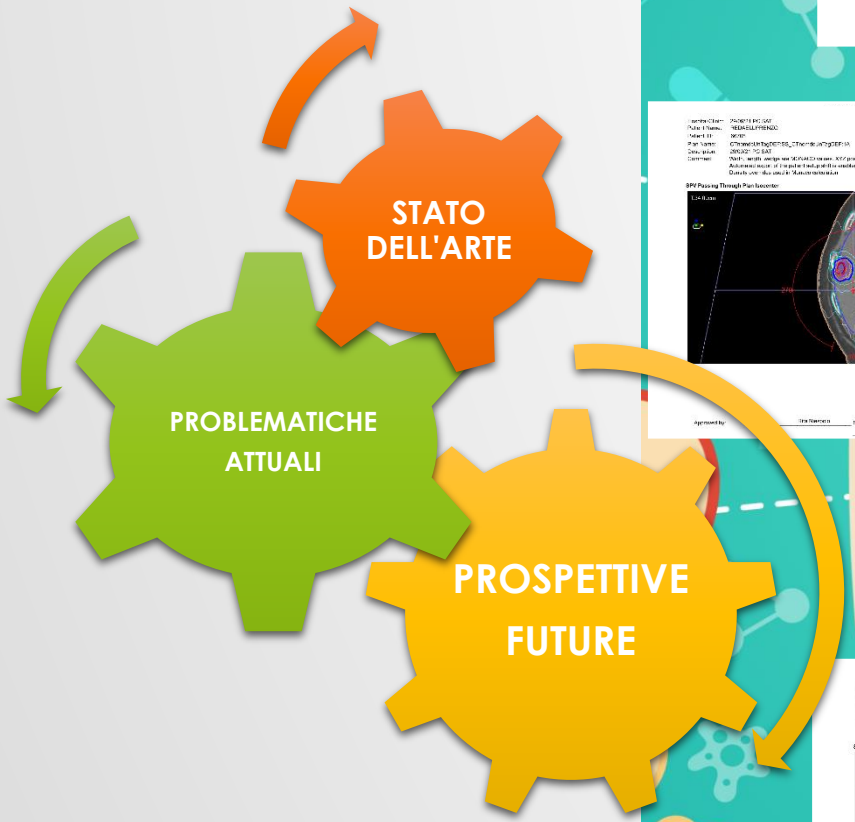
RADIOTERAPIA OGGI E DOMANI, 20 ANNI DELLA U.O.C. DI RADIOTERAPIA DELL'OSPEDALE MANZONI – LECCO

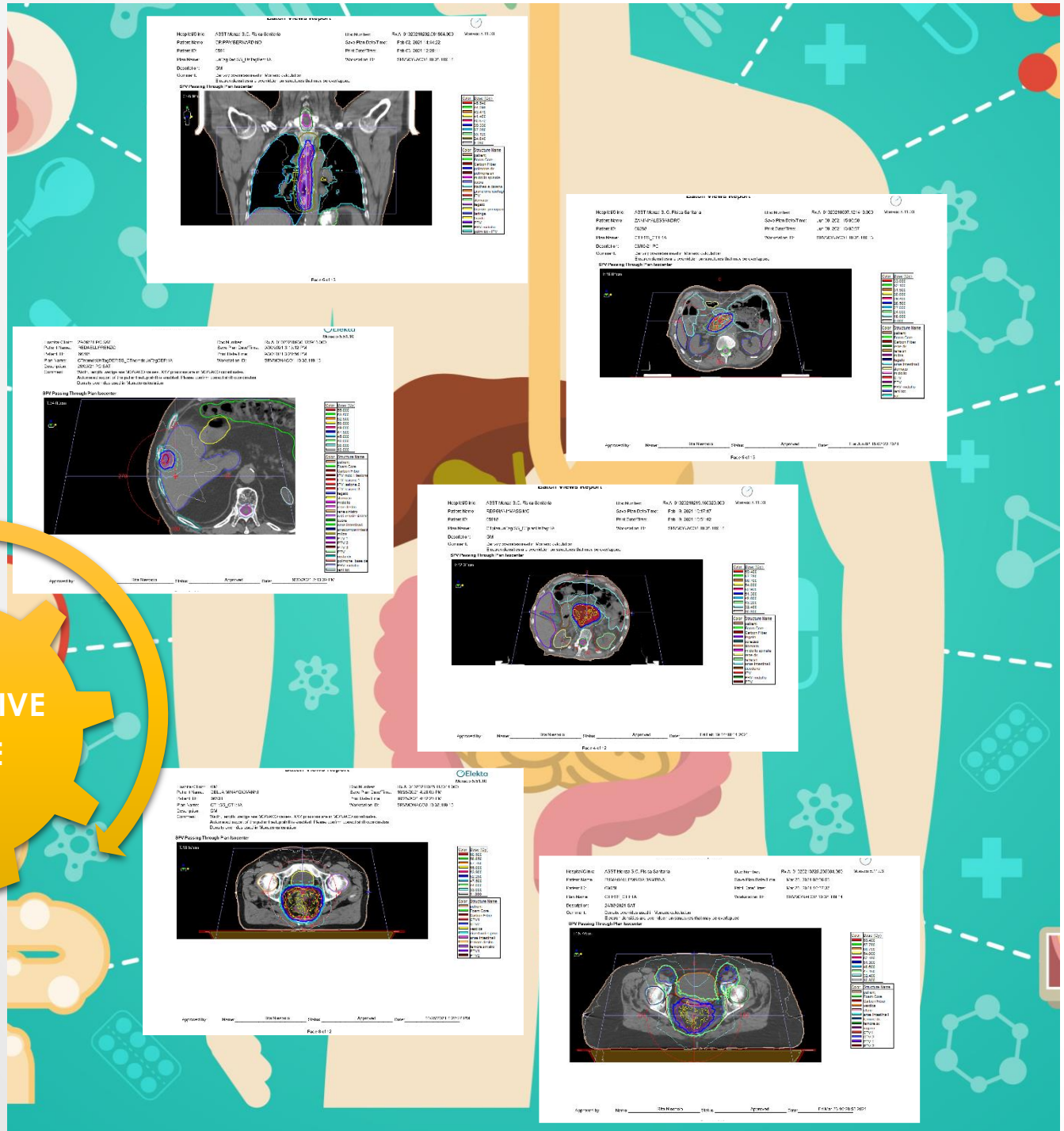
Stato dell’arte, problematiche attuali e prospettive future nel trattamento delle

Neoplasie dell’apparato Gastro-Enterico

RITA MARINA NIESPOLO
r.niespolo@asst-monza.it

Ospedale San Gerardo, Monza
Università degli Studi Milano-Bicocca


STATO DELL'ARTE
PROBLEMATICHE ATTUALI
PROSPETTIVE FUTURE



BMJ Best Practice

Help 0.53 CME / CPD

Search conditions, symptoms...

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English Português

Oesophageal cancer

View PDF

OVERVIEW	THEORY	DIAGNOSIS	MANAGEMENT	FOLLOW UP	RESOURCES
Summary	Epidemiology	Approach	Approach	Monitoring	Guidelines
	Aetiology	History and exam	Treatment algorithm	Complications	Images and videos
	Case history	Investigations	Emerging	Prognosis	References
		Differentials	Prevention		Patient leaflets
		Criteria	Patient discussions		idence
		Screening			

Last reviewed: 16 Oct 2021

Last updated: 09 Aug 2018

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Esophageal and Esophagogastric Junction Cancers

Version 4.2021 — August 03, 2021
NCCN.org

Continue

NCCN Guidelines for Patients® available at www.nccn.org/patients

NICE National Institute for Health and Care Excellence

NICE guideline

Oesophago-gastric cancer: assessment and management in adults

NICE guideline
Published: 24 January 2018
www.nice.org.uk/guidance/ng83

clinical practice guidelines

Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Lordick[1], C. Mariette[2], K. Haustermans[3], R. Obermannová[4] & D. A
Guidelines Committee*

[1]University Cancer Centre Leipzig, University Hospital Leipzig, Leipzig, Germany; [2]Department of Digestive and
France; [3]Department of Radiation Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, B
Memorial Cancer Institute and Faculty of Medicine, Masaryk University, Brno, Czech Republic; [5]Instituto C

Annals of Oncology 27 (Supplement 5): v50–v57, 2016
doi:10.1093/annonc/mdw329

half of the ESMO

Aiom Associazione Italiana di Oncologia Medica

Linee guida TUMORI DELL'ESOFAGO

Edizione 2019
Aggiornata a ottobre 2019

Esofago cervicale

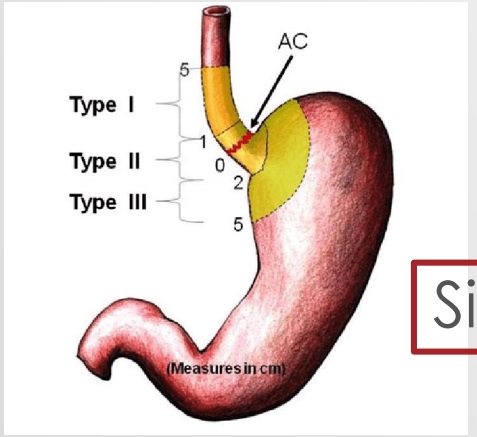
Malattia loco-regionale
(stadio I-III)

Carcinoma
squamocellulare (SCC)

ESOFAGO

Esofago toracico superiore/
medio

Adenocarcinoma (AC)



Esofago distale

Malattia localmente
avanzata non resecabile
o metastatica
(stadio IV)

Siewert I-II-III

VALUTAZIONE MULTIDISCIPLINARE

ALGORITMO TERAPEUTICO

ECOG </2
Paziente FIT per chirurgia o per radiochemioterapia

Carcinoma Squamocellulare
SCC

Adenocarcinoma
AC

pTis, pT1a

- **EMR (mucosectomia endoscopica)** → **sorveglianza endoscopica**
- **ESD (dissezione endoscopica sottomucosa)** → **sorveglianza endoscopica**
- **esofagectomia**

cT4b

- **CRT definitiva (RT 50-50.4Gy + CT)**
- **CT (se infiltrazione della trachea, grossi vasi, cuore)**

ALGORITMO TERAPEUTICO

ECOG </2
Paziente FIT per chirurgia o per radiochemioterapia

Carcinoma Squamocellulare SCC

- cT1b-T4a N0-N+
  - Esofago Cervicale → CRT definitiva → chirurgia di salvataggio
  - Esofago Toracico
    - CRT neoadiuvante (RT 41.4-50.4Gy + CT)
    - CRT definitiva (RT 50-50.4Gy + CT)
    - esofagectomia

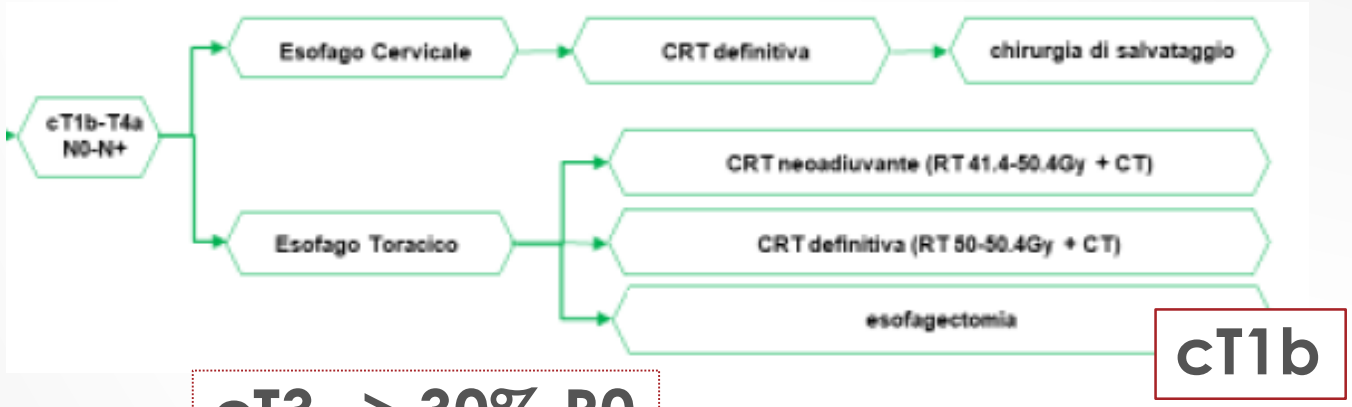
Adenocarcinoma AC

- cT1b-T4a N0-N+
  - CT perioperatoria
  - CRT neoadiuvante (RT 41.4-50.4Gy + CT)
  - CT neoadiuvante
  - esofagectomia

ALGORITMO TERAPEUTICO

ECOG </2
Paziente FIT per chirurgia o per radiochemioterapia

Carcinoma Squamocellulare
SCC



cT1b

Role of neoadjuvant treatment in clinical T2N0M0 oesophageal cancer: results from a retrospective multi-center European study

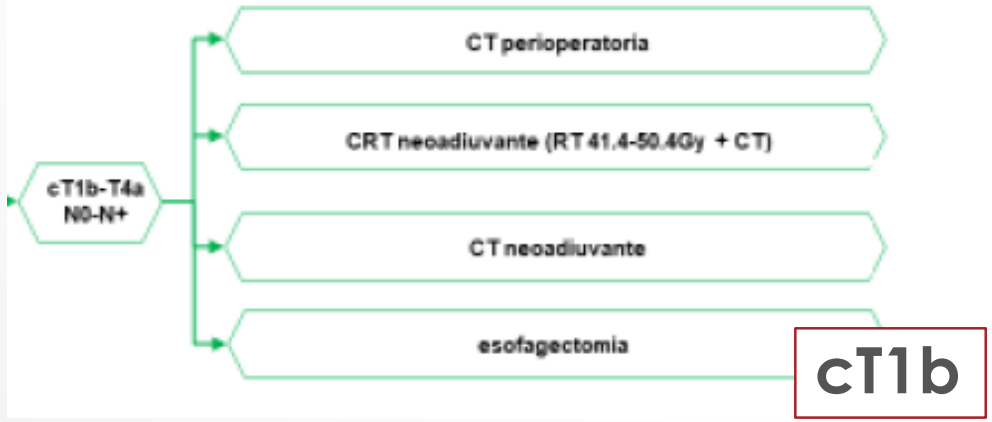
Eur J Cancer 2016

Sheraz R. Markar, Caroline Gronnier, Arnaud Pasquer, Alain Duhamel, Hélène Beal, Jérémie Théreaux, Johan Gagnière, Gil Lebreton, Cécile Brigand, Bernard Meunier, Denis Collet, Christophe Mariette on behalf of the FREGAT working group – FRENCH – AFC[1]

[1] See Appendix B .

cT3 -> 30% R0

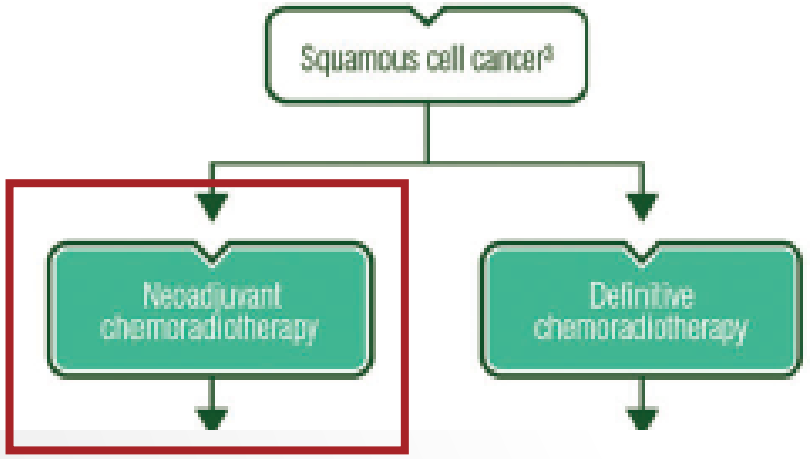
Adenocarcinoma
AC

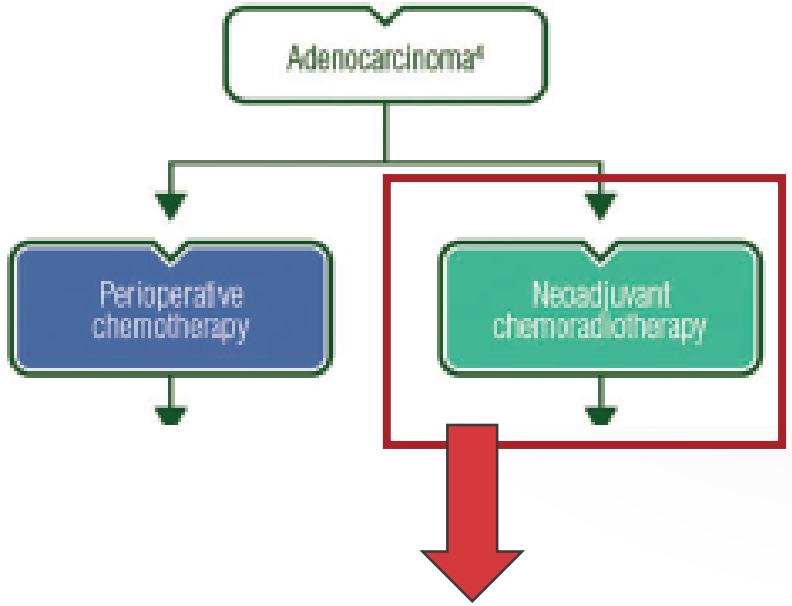


cT1b

Recidive locoregionali: 30-40%

5yOS: <35% (<20% se localmente avanzata)





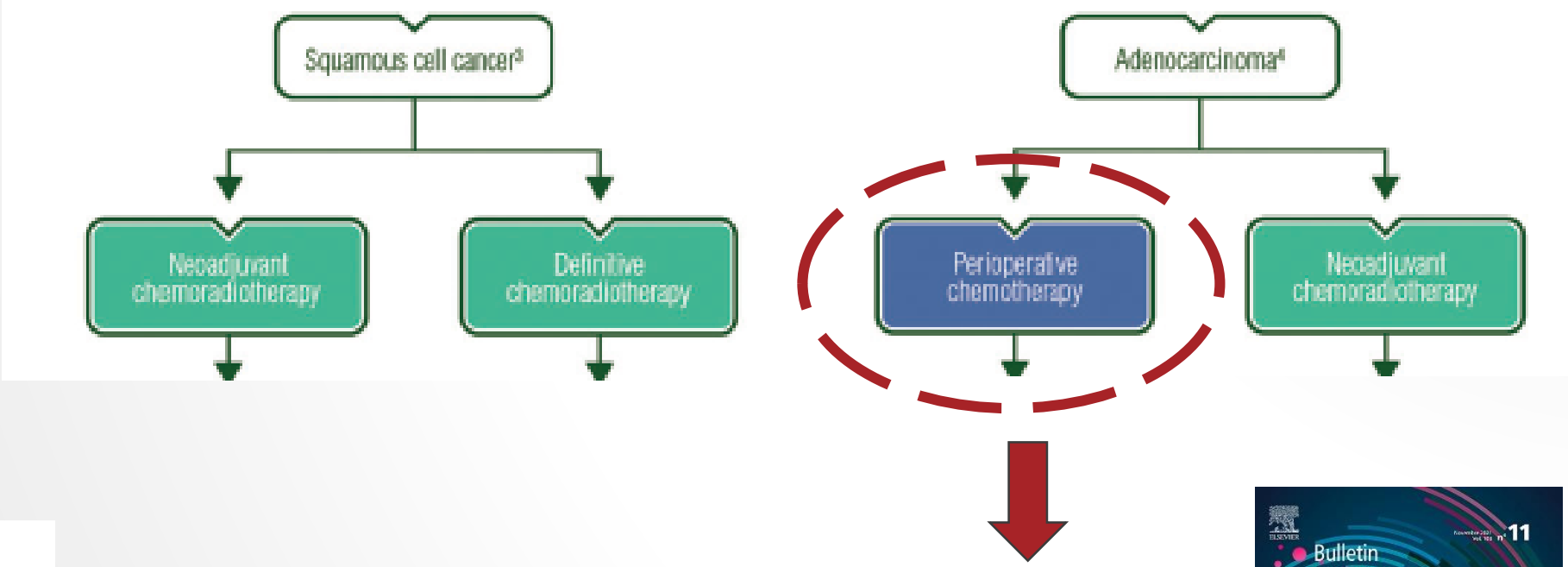
Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

Joel Shapiro, J Jan B van Lanschot, Maarten C C M Hulshof, Pieter van Hagen, Mark I van Berge Henegouwen, Bas P L Wijnhoven, Hanneke W M van Laarhoven, Grard A P Nieuwenhuijzen, Geke A P Hospers, Johannes J Bonenkamp, Miguel A Cuesta, Reinoud J B Blaisse, Olivier R C Busch, Fiebo J W ten Kate, Geert-Jan M Creemers, Cornelis J A Punt, John Th M Plukker, Henk M W Verheul, Ernst J Spillenaar Bilgen, Herman van Dekken, Maurice J C van der Sangen, Tom Rozema, Katharina Biermann, Jannet C Beukema, Anna H M Piet, Caroline M van Rij, Janny G Reinders, Hugo W Tilanus, Ewout W Steyerberg, Ate van der Gaast, for the CROSS study group

carboplatin and paclitaxel for 5 weeks and concurrent radiotherapy 41.4 Gy in 23 fractions

Recidive locoregionali: 30-40%

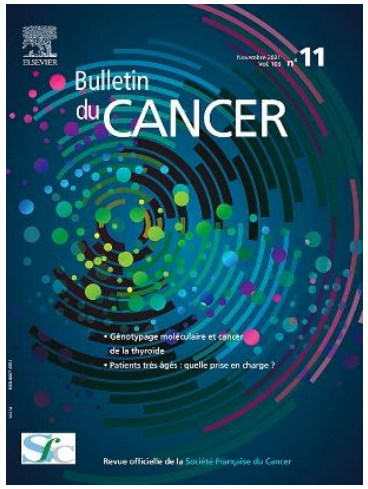
5yOS: <35% (<20% se localmente avanzata)



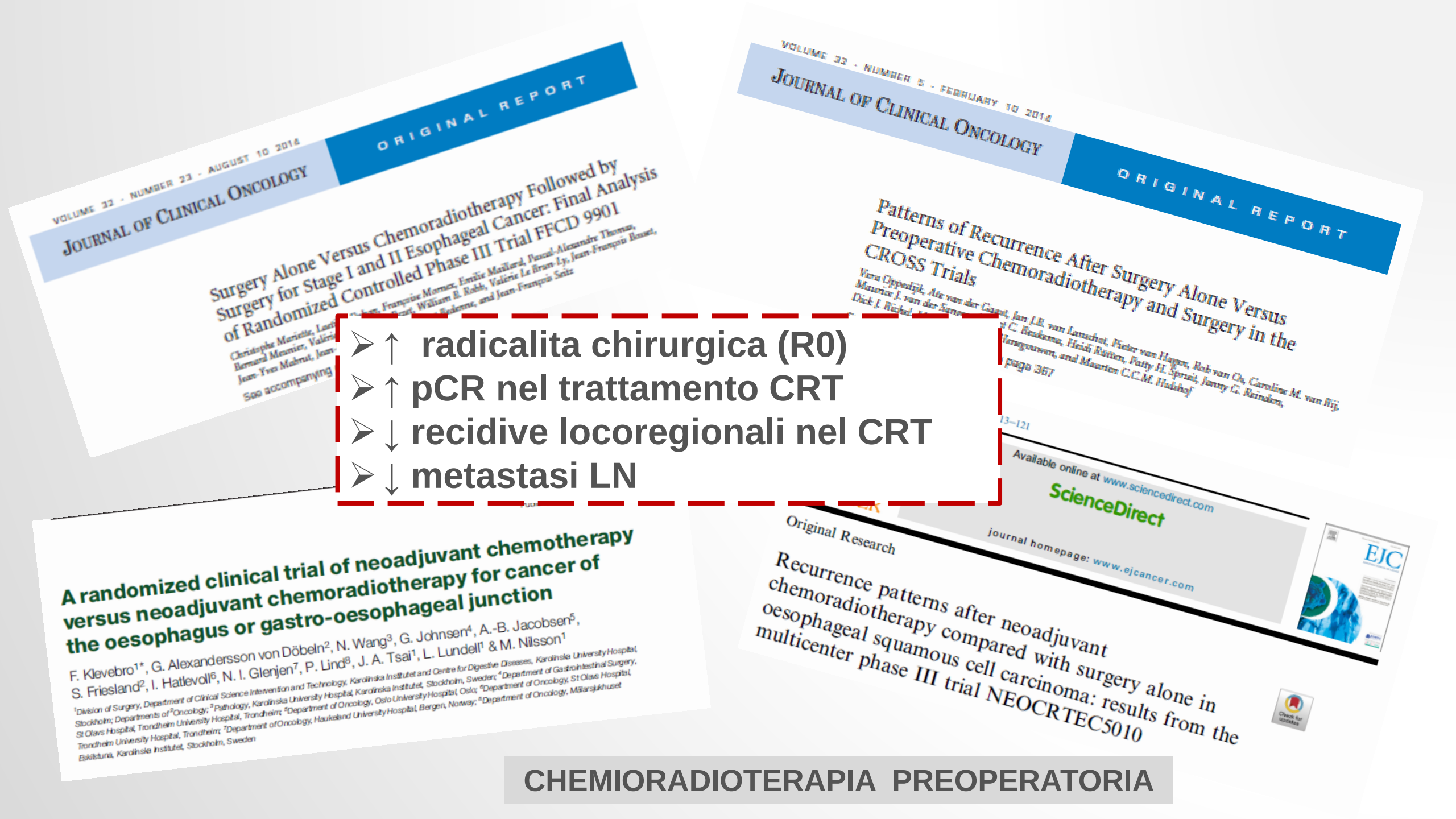
[Does the FLOT regimen a new standard of perioperative chemotherapy for localized gastric cancer?]

[Article in French]

Antoine Adenis [1], Emmanuelle Samalin [2], Thibault Mazard [2], Fabienne Portales [2], Anne Mourregot [2], Marc Ychou [3]



(FLOT: fluorouracil plus leucovorin, oxaliplatin and docetaxel)


VOLUME 32 · NUMBER 23 · AUGUST 10 2014
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT
Surgery Alone Versus Chemoradiotherapy Followed by Surgery for Stage I and II Esophageal Cancer: Final Analysis of Randomized Controlled Phase III Trial FFCD 9901
VOLUME 32 · NUMBER 5 · FEBRUARY 10 2014
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT
Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials
➢ ↑ radicalita chirurgica (R0)
➢ ↑ pCR nel trattamento CRT
➢ ↓ recidive locoregionali nel CRT
➢ ↓ metastasi LN
A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction
Available online at www.sciencedirect.com
ScienceDirect
journal homepage: www.ejcancer.com
EJC
Original Research
Recurrence patterns after neoadjuvant chemoradiotherapy compared with surgery alone in oesophageal squamous cell carcinoma: results from the multicenter phase III trial NEOCRTEC5010
CHEMIORADIOTERAPIA PREOPERATORIA

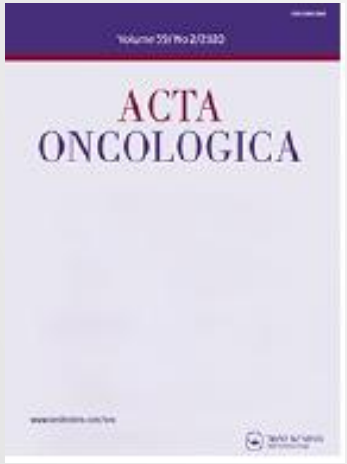
ACTA ONCOLOGICA
2021, VOL. 60, NO. 4, 497–504
https://doi.org/10.1080/0284186X.2020.1870246

Taylor & Francis
Taylor & Francis Group

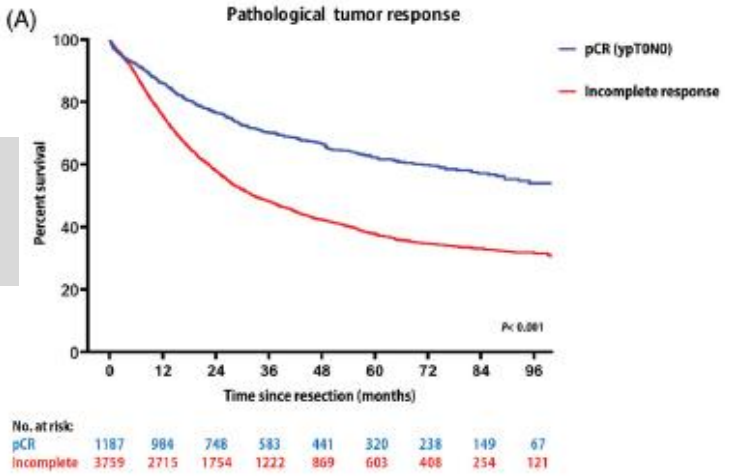
ORIGINAL ARTICLE

OPEN ACCESS Check for updates

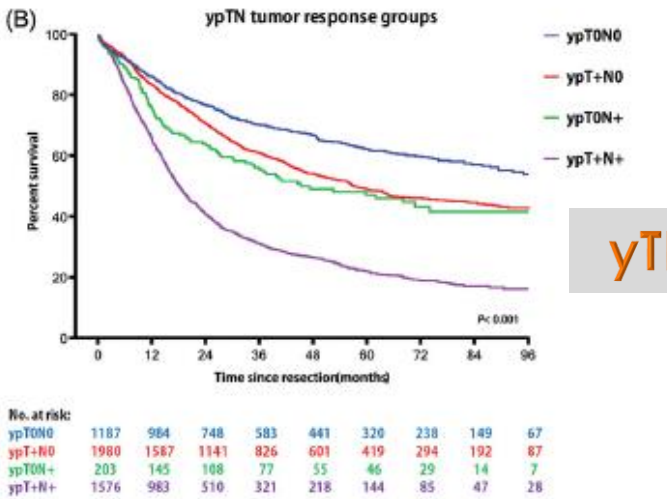
Impact of pathological tumor response after CROSS neoadjuvant chemoradiotherapy followed by surgery on long-term outcome of esophageal cancer: a population-based study



OS



yTN/os



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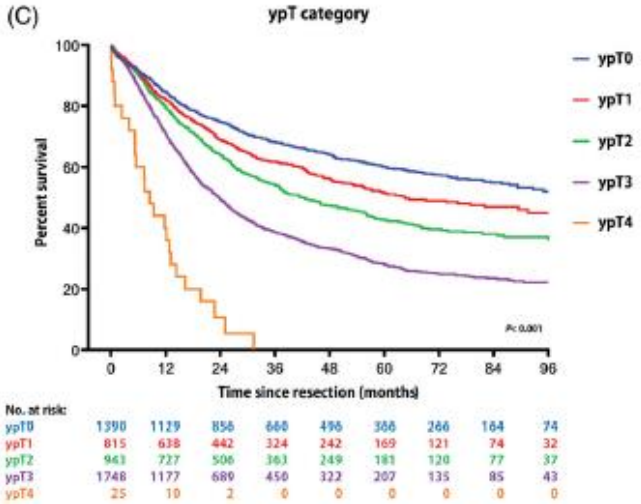
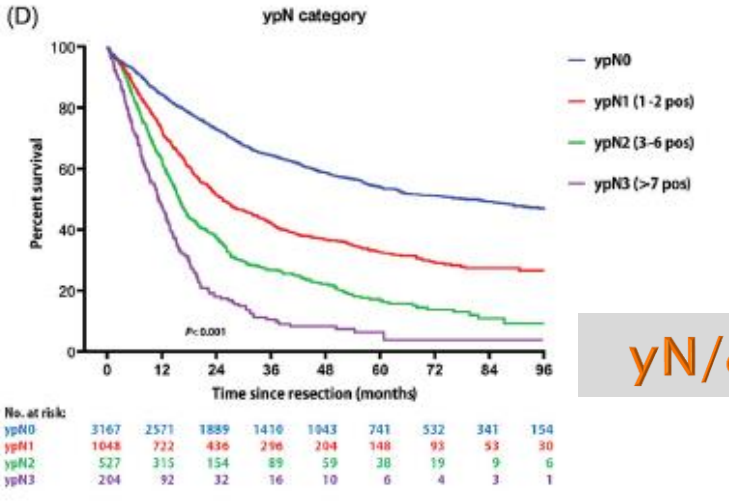


yN/os



Li et al. BMC Surg (2021) 21:137
https://doi.org/10.1186/s12893-021-01136-z

BMC Surgery

RESEARCH ARTICLE Open Access

Neoadjuvant chemoradiotherapy improves survival in locally advanced adenocarcinoma of esophagogastric junction compared with neoadjuvant chemotherapy: a propensity score matching analysis

Jing Li[1†], Qun Zhao[2†], Xueke Ge[1], Yuzhi Song[1], Yuan Tian[2], Shuoshuo Wang[1], Ming Liu[1] and Xueying Qiao[1*]

- neoadjuvant chemotherapy capecitabine plus oxaliplatin
- neoadjuvant chemoradiotherapy capecitabine plus oxaliplatin with concurrent radiotherapy Intensity-modulated radiation therapy (IMRT) (total dose of PTV: 45 Gy).

Siewert II and III

OS	CRT	CT
1 anno	84,8%	55%
3 anni	78,3%	38,3%

PFS	CRT	CT
1 anno	84,9%	49,2%
3 anni	68,3%	29%

pCR	CRT	CT
	17%	1,9%

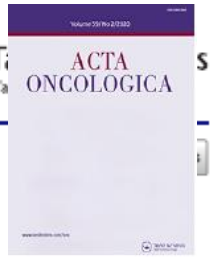
NO LR

LR	CRT	CT
	3,8%	26,9%

DM	CRT	CT
	20,8%	23.1%

LR + DM	CRT	CT
	3,8%	7,7%

ACTA ONCOLOGICA
2020, VOL. 59, NO. 2, 233–236
https://doi.org/10.1080/0284186X.2019.1698765



LETTER TO THE EDITOR

Gastro-oesophageal junction: to FLOT or to CROSS?

Tom van den Ende[a], Maarten C. C. M. Hulshof[b], Mark I. van Berge Henegouwen[c], Martijn G. H. van Oijen[a] and Hanneke W. M. van Laarhoven[a]

Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial

CROSS or FLOT in Distal Esophageal and Gastroesophageal Cancer

Ibrahim Karadag, Serdar Karakaya, Ozturk Ates and Omur Berna Cakmak Oksuzoglu

Department of Medical Oncology, Dr. A.Y. Ankara Oncology Traininig and Research Hospital, Turkey

(German Gastric Group at AIO).Abstract LBA27_PR. ESMO 2017.

Cancer. *J Coll Physicians Surg Pak* 2021; **31(03)**:326-329.

Conclusion: Postoperative pathological response rate in the CROSS group was significantly higher compared to the FLOT group. CROSS and FLOT protocols contributed to survival similarly in patients with GEJ ADC, hematological side effects were more pronounced in patients receiving CRT.

BMC Cancer

STUDY PROTOCOL Open Access

EORTC-1203-GITCG - the "INNOVATION"-trial: Effect of chemotherapy alone versus chemotherapy plus trastuzumab, versus chemotherapy plus trastuzumab plus pertuzumab, in the perioperative treatment of HER2 positive, gastric and gastroesophageal junction adenocarcinoma on pathologic response rate: a randomized phase II-intergroup trial of the EORTC-Gastrointestinal Tract Cancer Group, Korean Cancer Study Group and Dutch Upper GI-

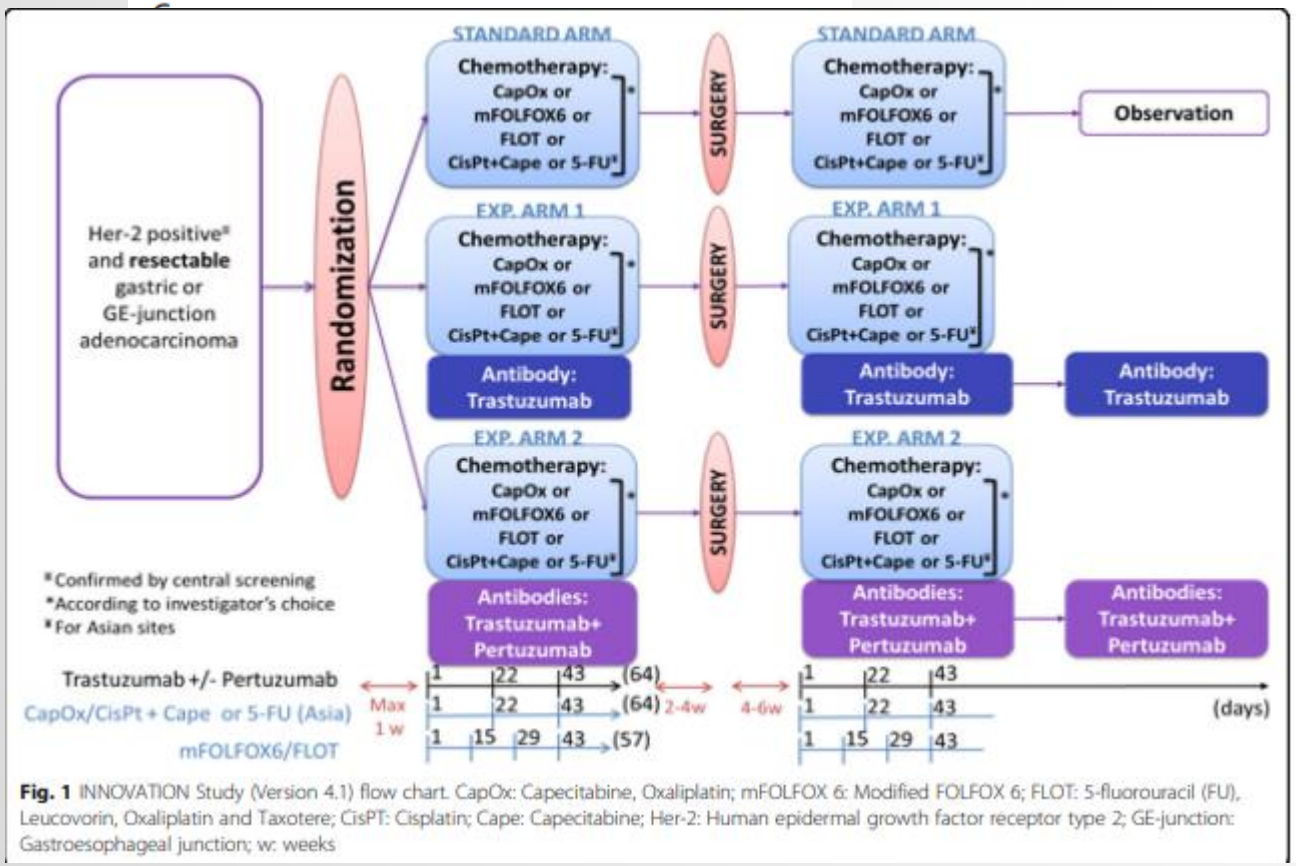


Fig. 1 INNOVATION Study (Version 4.1) flow chart. CapOx: Capecitabine, Oxaliplatin; mFOLFOX 6: Modified FOLFOX 6; FLOT: 5-fluorouracil (FU), Leucovorin, Oxaliplatin and Taxotere; CisPT: Cisplatin; Cape: Capecitabine; Her-2: Human epidermal growth factor receptor type 2; GE-junction: Gastroesophageal junction; w: weeks

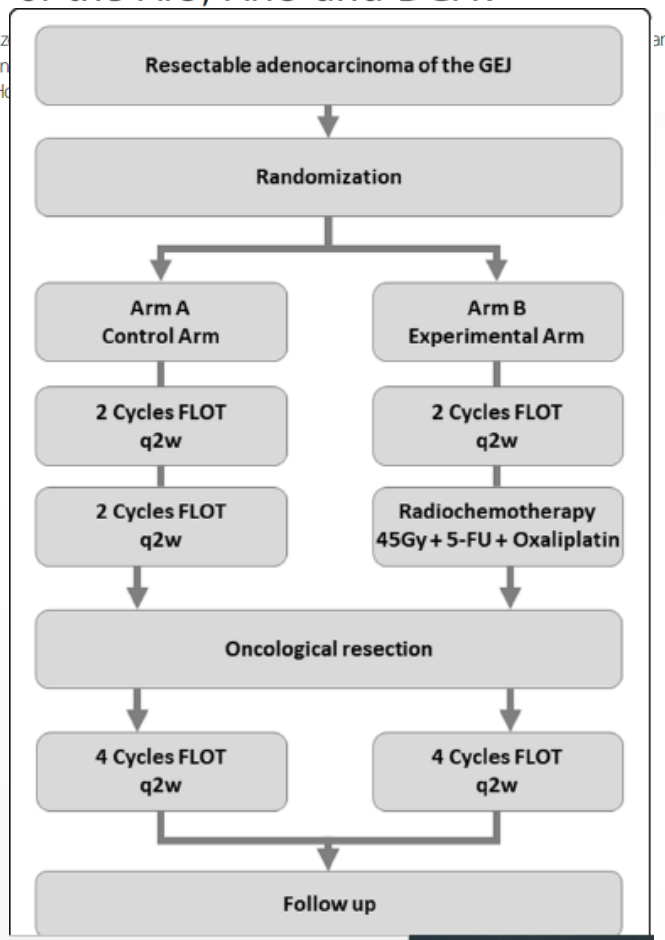
Lorenzen *et al. BMC Cancer* (2020) 20:886
https://doi.org/10.1186/s12885-020-07388-x

BMC Cancer

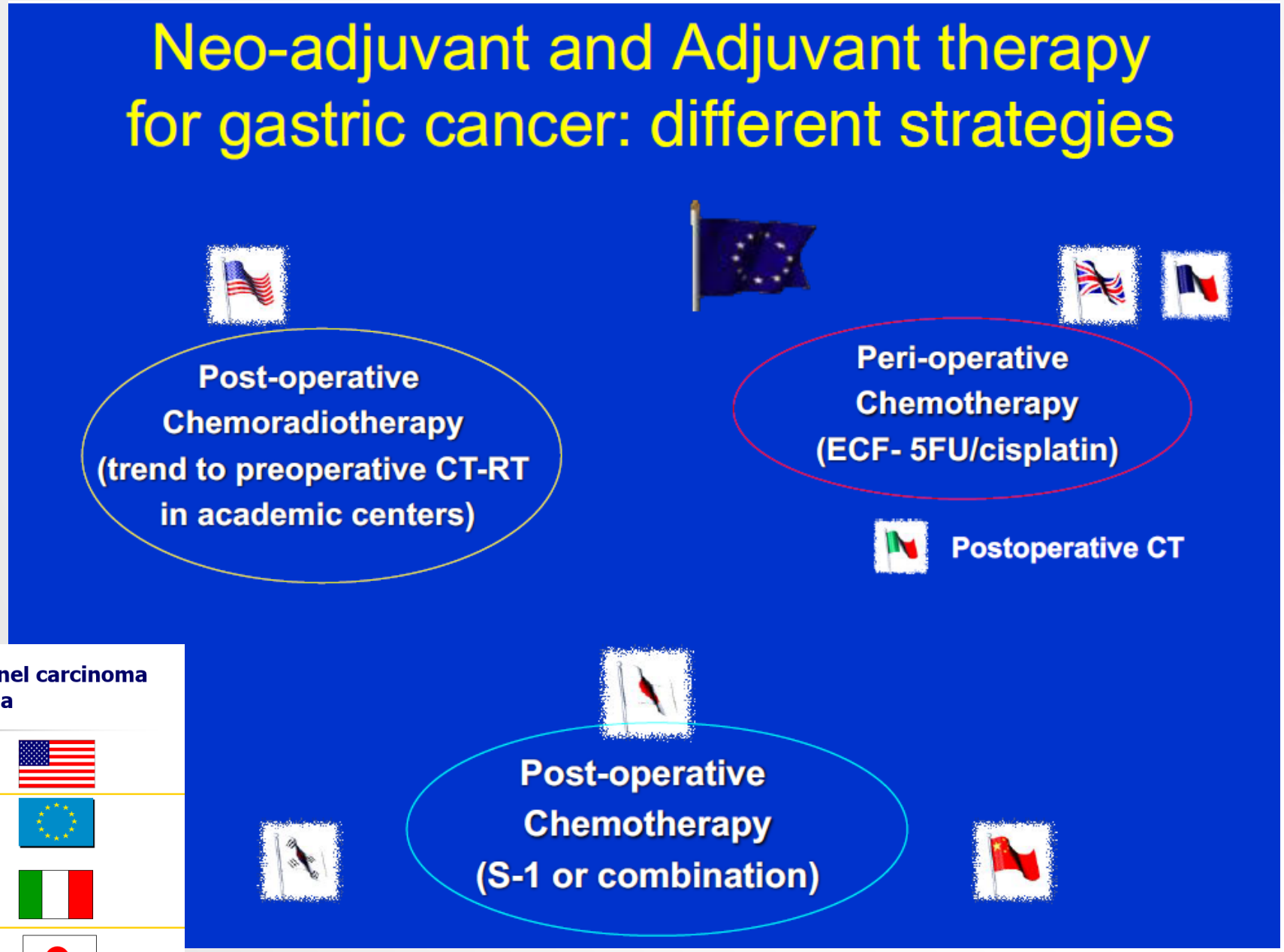
STUDY PROTOCOL Open Access

RACE-trial: neoadjuvant radiochemotherapy versus chemotherapy for patients with locally advanced, potentially resectable adenocarcinoma of the gastroesophageal junction - a randomized phase III joint study of the AIO, ARO and DGAV

Sylvie Lorenz
Frederik Wen
Ralf-Dieter Ho
an Mönig[4],

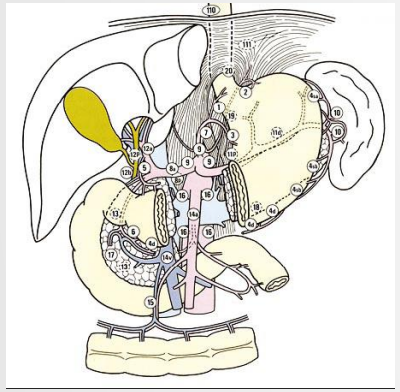


Neo-adjuvant and Adjuvant therapy for gastric cancer: different strategies



La terapia adiuvante nel carcinoma gastrico: le linee guida

- **Stati Uniti: CT/RT**
- **Europa CT**
- **Italia CT**
- **Giappone S-D3**



La prognosi nel carcinoma gastrico

Category	R0-Status (%)
pT1	98,2
pT2	86,7
pT3	59,7
pT4	40,6

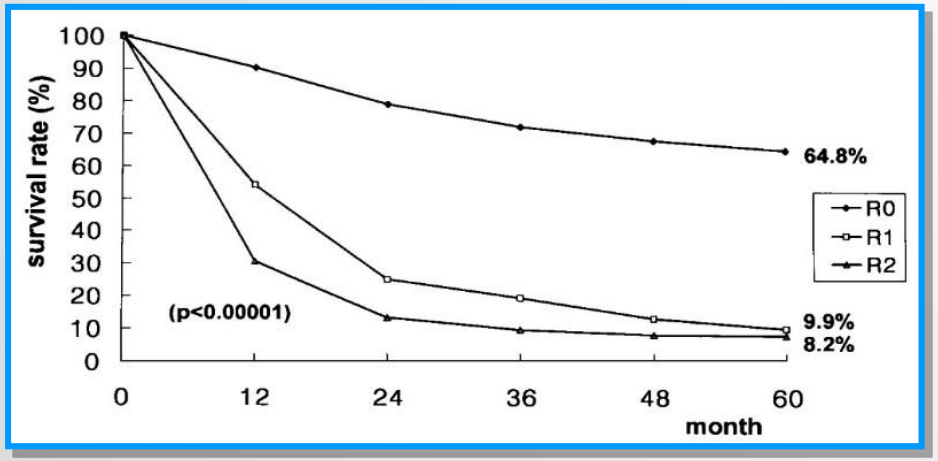
Siewert et al. Ann Surg 1998; 228: 449-461

VOLUME 23 · NUMBER 28 · OCTOBER 1 2005
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

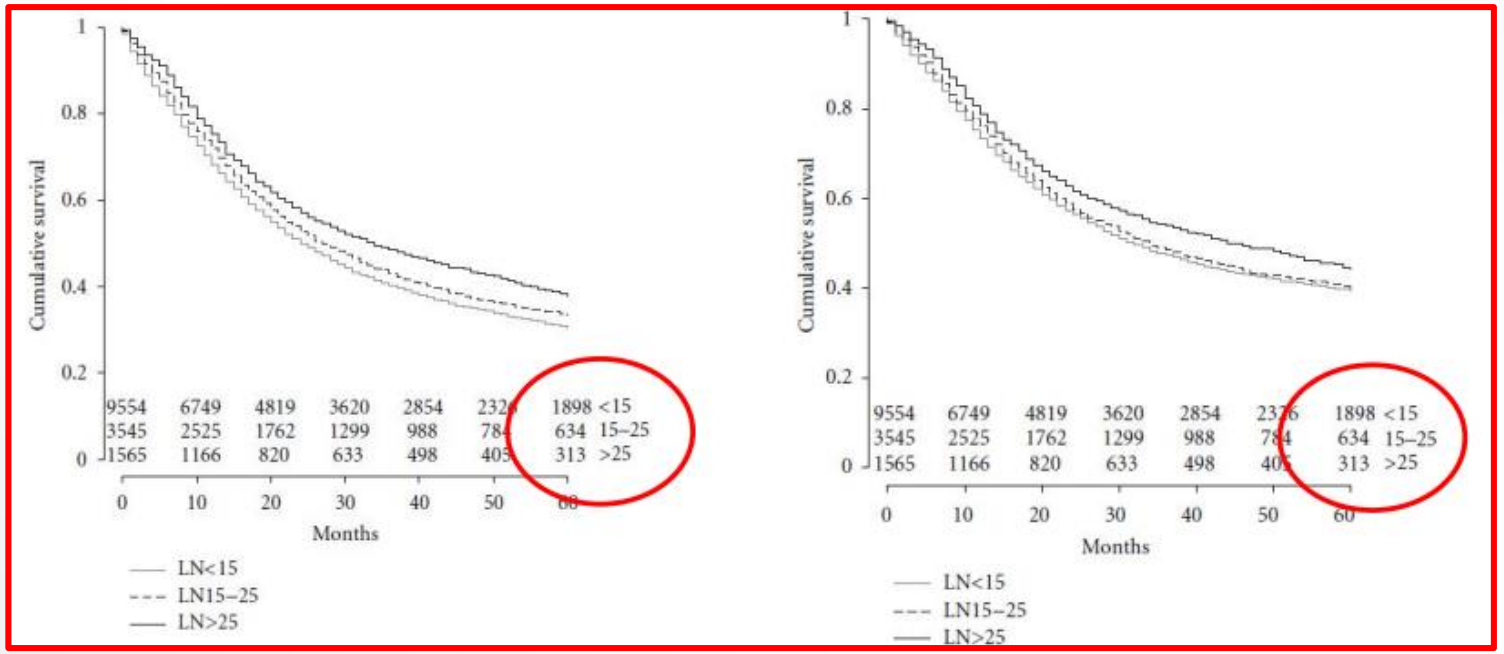
Impact of Total Lymph Node Count on Staging and Survival After Gastrectomy for Gastric Cancer: Data From a Large US-Population Database

David D. Smith, Rebecca R. Schwarz, and Roderich E. Schwarz

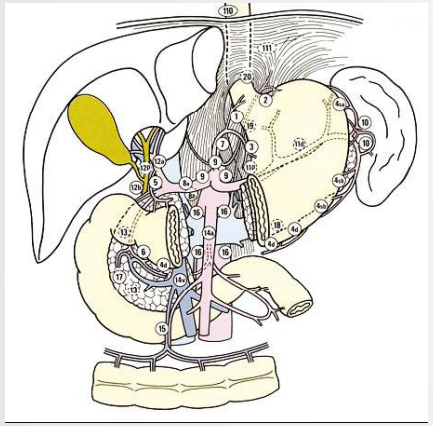
SVV correlata alla resezione



SVV correlata al tipo di linfoadenectomia



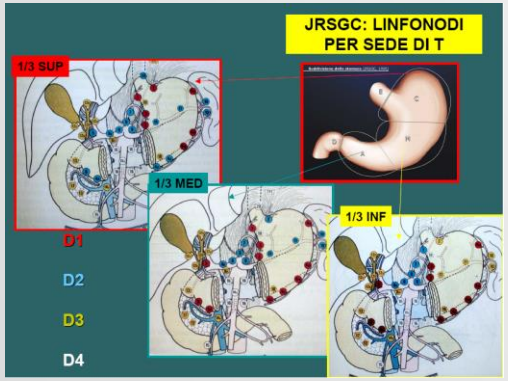
International Journal of Surgical Oncology
Volume 2012, Article ID 307670, 7 pages



Radioterapia adiuvante quale ruolo nella pratica clinica?

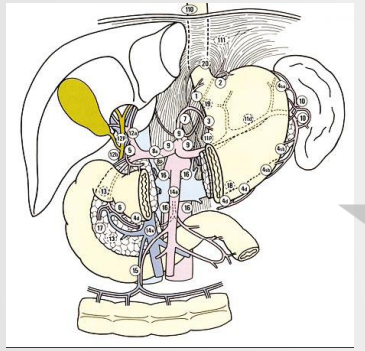
A. Nei pazienti con R1 , R2

B. Nei pazienti che hanno ricevuto una linfoadenectomia insufficiente
<15 linfonodi se N negativi e T3
(soprattutto se invasione vascolare)
<25 linfonodi se N positivi
(ovviamente dipende da eta' e condizioni generali)

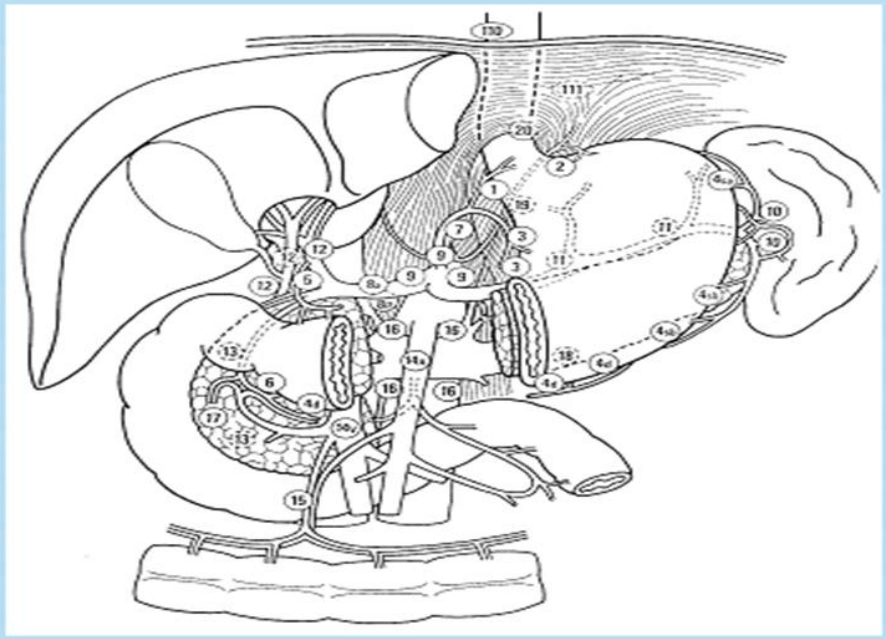


<u>Classificazione dei linfonodi della Japanese Research Society for Gastric Cancer del 1981</u>

- Fa riferimento al drenaggio linfatico in funzione della sede di origine del tumore nello stomaco, suddiviso in 3 parti: superiore, media ed inferiore.
- Gli Autori giapponesi hanno inoltre classificato l'estensione della linfoadenectomia in D1, D2 e D3 in rapporto alle stazioni linfonodali asportate

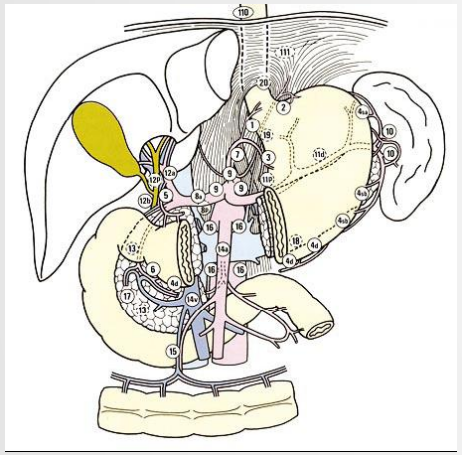


D2



Sistema Giapponese Classificazione dei linfonodi regionali		
Paracardiale dx 1	Arteria epatica comune 8	Vasi colici medi 15
Paracardiale sn 2	Tripode celiaco 9	Paraaortici 16
Piccola curva 3	Ilo splenico 10	Faccia anteriore della testa del pancreas 17
Grande curva 4	Arteria splenica 11	Margine inferiore del pancreas 18
Sovrapilorici 5	Ligamento epatoduodenale 12	Sottodiaframmatici 19
Sottopilorici 6	Faccia posteriore del pancreas 13	Iato esofageo 20
Arteria gastrica sn 7	Radice del mesentere 14	

livello	sede	Linfoadenectomia per stazione
D2	III inferiore III medio III superiore	1,3,4(d,sb),5,6,7,8,9,11p,12a, 14v 1,2,3,4,5,6,7,8a,9,11p 1,2,3,4,5,6,7,8a,9,11
D3	III inferiore III medio III superiore	D2+ 8p,12p,13,16 D2+ 8p,12p,13,16 D2+ 8p,12p,13,16



GIRCG (Gruppo Italiano di Ricerca Cancro Gastrico)
Trattamento Cancro Gastrico Avanzato

Stadio 0	Tis N0 M0
Stadio I a	T1 N0 M0
Stadio I b	T1 N1 M0 - T2 N0 M0
Stadio II	T1 N2 M0 - T2 N1 M0 - T3 N0 M0
Stadio III a	T2 N2 M0 - T3 N1 M0 - T4 N0 M0
Stadio III b	T3 N1 M0 - T4 N2 M0
Stadio IV	T4 N2 M0 - ogni T ogni N M1

1) In una **Linfoadenectomia D1** viene asportato un numero di linfonodi variabile tra 15 e 18

2) Mentre in una **dissezione D2** ne vengono asportati mediamente tra 31 e 35 linfonodi, (in alcune casistiche 25-30)

1) Viene definita **Linfoadenectomia over-D1** , quando si asportano i linfonodi perigastrici, quelli lungo i grandi vasi e lungo i primi centimetri dell'arteria splenica → (la linfoadenectomia dell'ilo splenico e del peduncolo epatico è opzionale)

CHEMORADIOTHERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

JOHN S. MAC ... AHL, M.D.,
NORMAN (... II, M.D.,
LE ...

N Engl J Med, Vol. 345, No. 10 · September 6, 2001

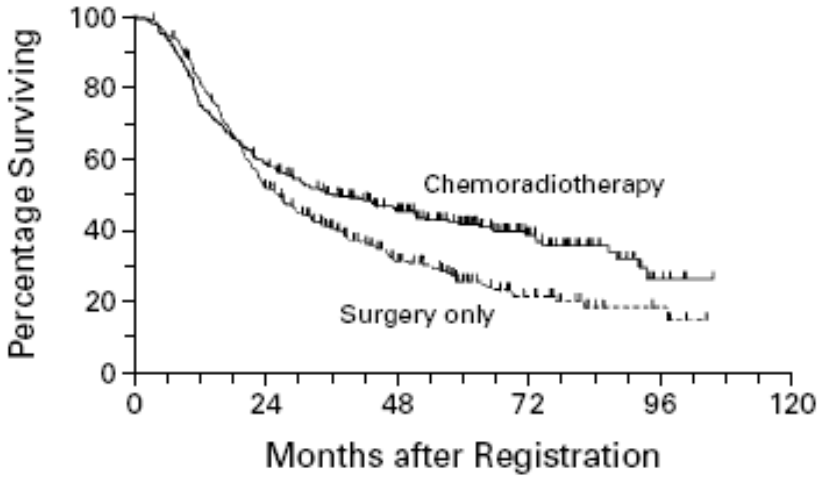


Figure 1. Overall Survival among All Eligible Patients, Accord-

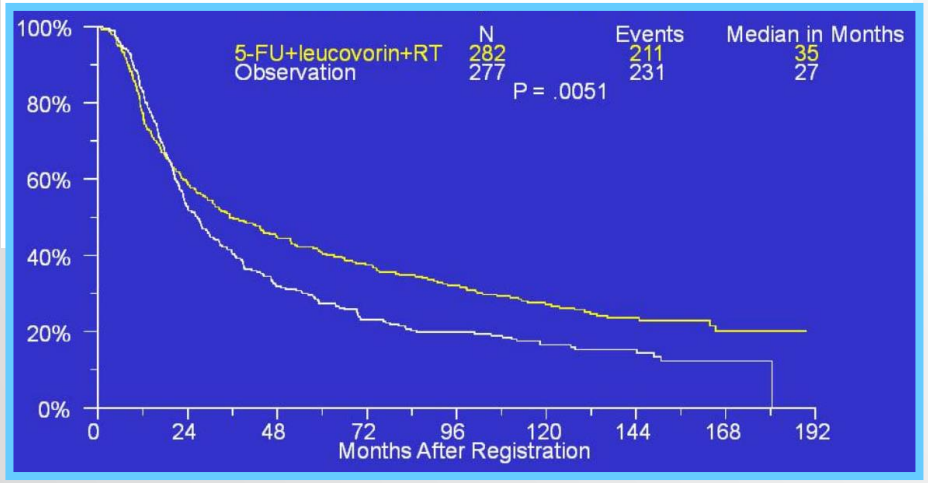
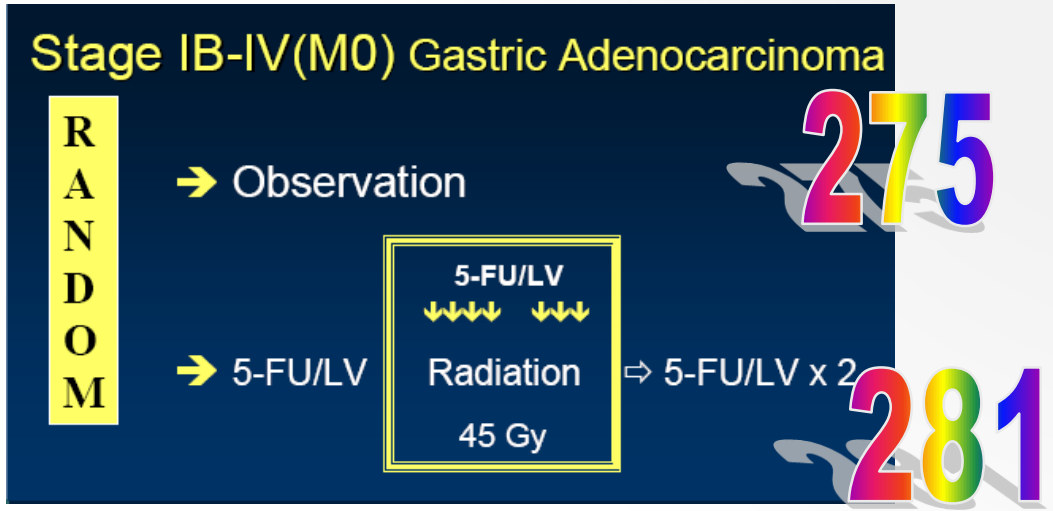


TABLE 4. SITES OF RELAPSE.*

SITE	PATIENTS WITH RELAPSES	
	SURGERY-ONLY GROUP (N=177)	CHEMORADIOTHERAPY GROUP (N=120)
	no. (%)	
Local	51 (29)	23 (19)
Regional	127 (72)	78 (65)
Distant	32 (18)	40 (33)

*Because patients could have relapses at multiple sites, the total numbers of relapses are greater than the numbers of patients in each group who had relapses.

Macdonald JS, ASCO 2009



10% D2 (54 pazienti)

36% D1

54% D0

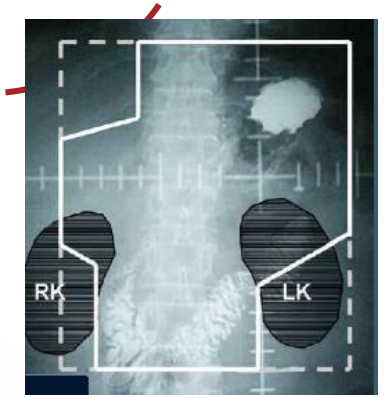
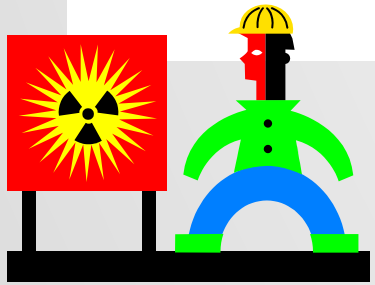


TABLE 2. REASONS FOR THE CESSATION OF CHEMORADIOTHERAPY AMONG THE 281 PATIENTS IN THE CHEMORADIOTHERAPY GROUP.

REASON FOR CESSATION	NO. OF PATIENTS (%)
Protocol treatment completed	181 (64)
Toxic effects	49 (17)
Patient declined further treatment	23 (8)
Progression of disease	13 (5)
Death	3 (1)
Other	12 (4)



60 % del volume epatico con 30 Gy
> 30 % volume cardiaco con 40 Gy

Nel protocollo INT-0116 ci furono il 35% di deviazioni al protocollo radioterapico

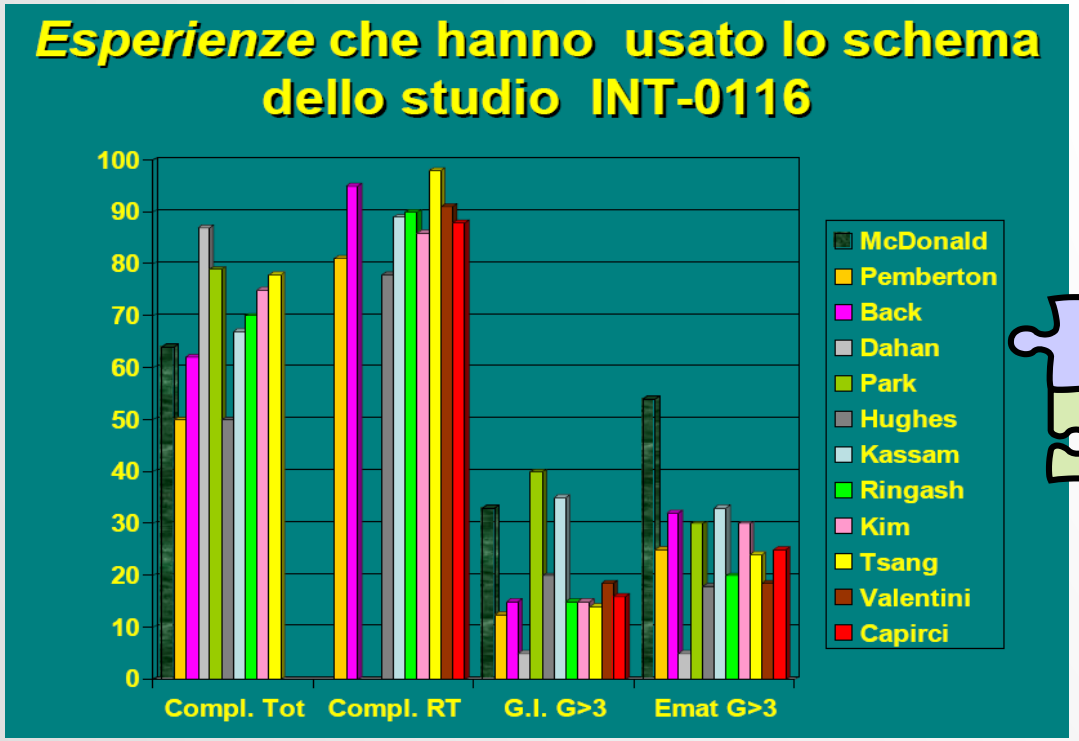
TABLE 3. MAJOR TOXIC EFFECTS OF CHEMORADIOTHERAPY.*

TYPE OF TOXIC EFFECT	NO. OF PATIENTS (%)
Hematologic	148 (54)
Gastrointestinal	89 (33)
Influenza-like	25 (9)
Infection	16 (6)
Neurologic	12 (4)
Cardiovascular	11 (4)
Pain	9 (3)
Metabolic	5 (2)
Hepatic	4 (1)
Lung-related	3 (1)
Death†	3 (1)

*Major toxic effects were defined as those of grade 3 or higher. Data are for the 273 patients who received chemoradiotherapy.

†One patient died from a cardiac event, one from sepsis complicating myelosuppression, and one from pulmonary fibrosis.

RISPOSTA ALLE CRITICHE RELATIVE ALLA TOSSICITÀ



PERCHÉ TANTA DIVERSITÀ CON LO STESSO SCHEMA TERAPEUTICO?

VARIABILITA´ DELLA RADIOTERAPIA

DEFINIZIONE DEL VOLUME BERSAGLIO


Radiotherapy and Oncology 92 (2009) 164–175

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

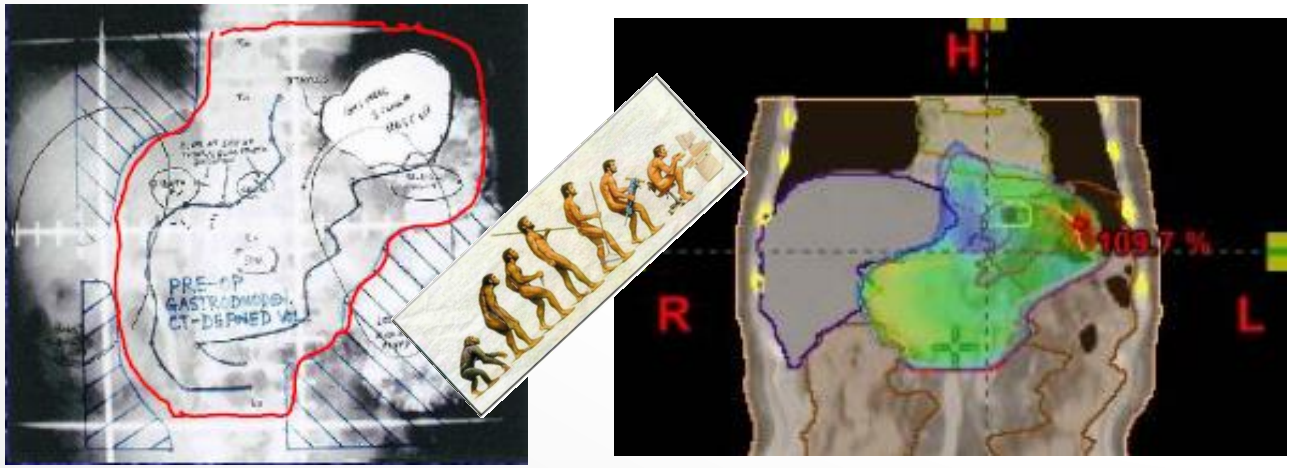
ELSEVIER

Guidelines

EORTC-ROG expert opinion: Radiotherapy volume and treatment guidelines for neoadjuvant radiation of adenocarcinomas of the gastroesophageal junction and the stomach

Oscar Matzinger [a,b,*], Erich Gerber [c], Zvi Bernstein [d], Philippe Maingon [e], Karin Haustermans [f], Jean François Bosset [g], Akos Gulyban [a], Philip Poortmans [h], Laurence Collette [a], Abraham Kuten [d]

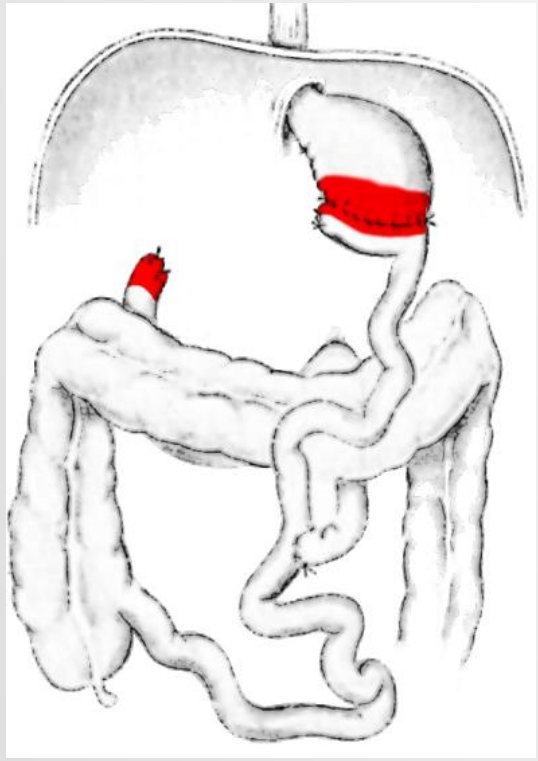
TECNICHE DI TRATTAMENTO

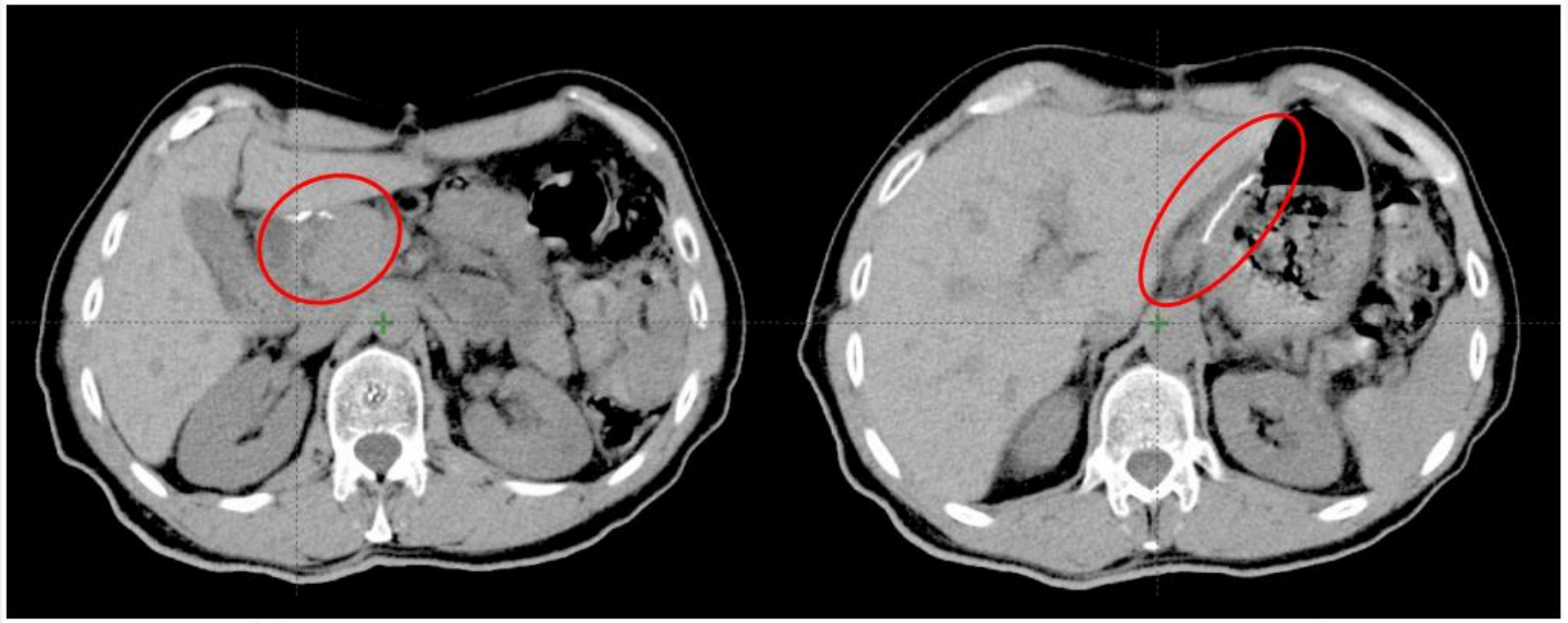


Postop CT-RT: Possible benefit, however, limitations…

Area at Risk: Anastomosis & Stump

Partial gastrectomy: Y sec Roux



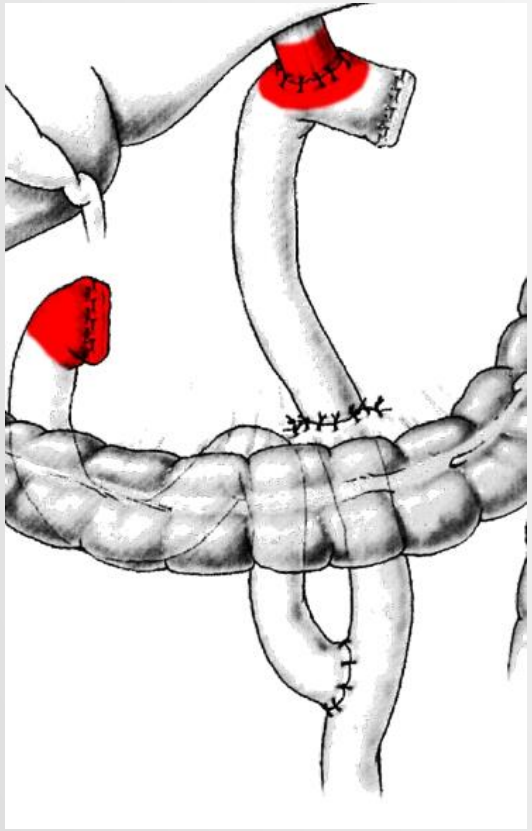


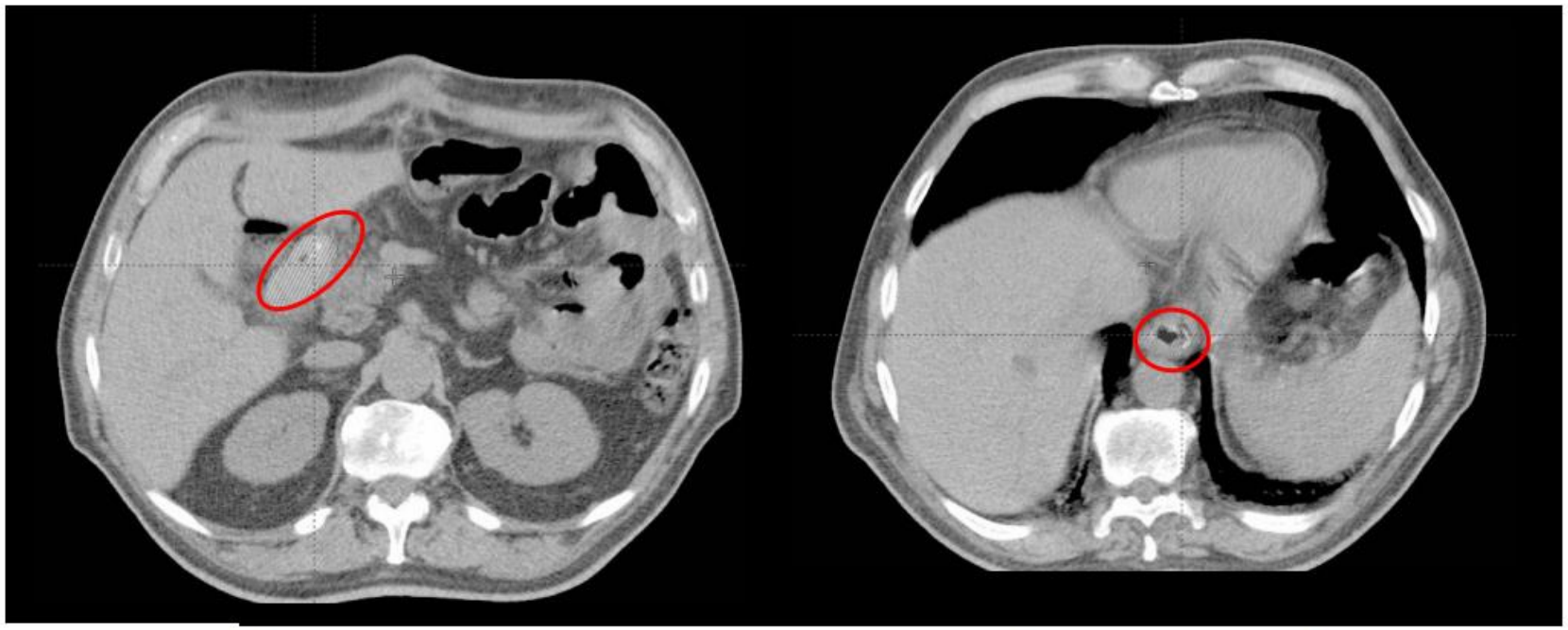
Stump *Anastomosis*

Postop CT-RT: Possible benefit, however, limitations…

Area at Risk: Anastomosis & Stump

Total gastrectomy: Y sec Roux





Stump

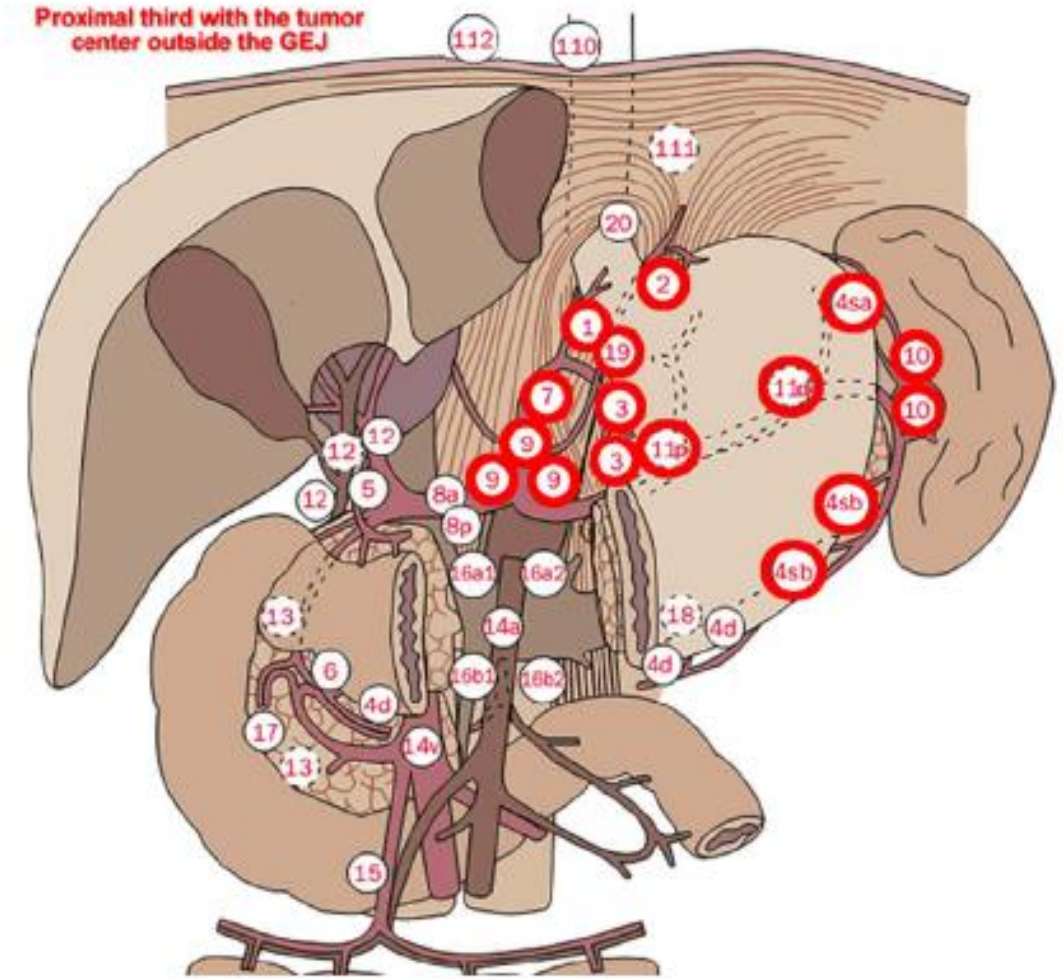
Anastomosis

CRITICITÀ NELL'IDENTIFICAZIONE DELLE STAZIONI LINFONODALI

- ***RT post-operatoria***

1. Carente descrizione delle procedure chirurgiche
2. Alterazioni anatomiche legate alla chirurgia
3. Mancanza di clips
4. Sovrapposizioni di volumi (es. letto operatorio con stazioni linfonodali
5. Carente acquisizione di TC di simulazione (mdc)

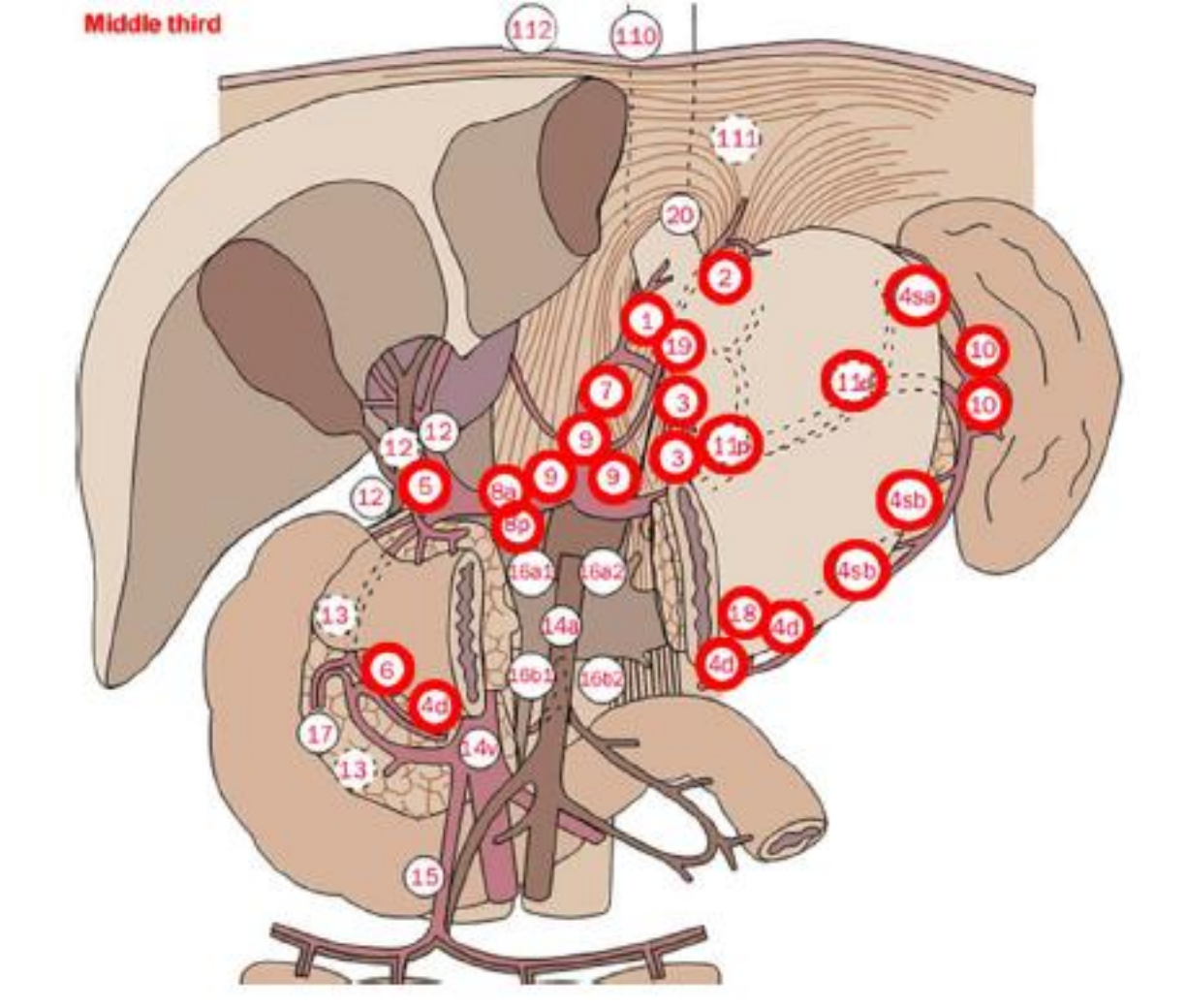
TUMORE DEL 1/3 PROSSIMALE : N



Paraesofagei
Cardiali
Piccola e grande curvatura
Antro e Piloro
Arteria splenica ed ilo splenico
Catena retropancreatica superiore
Arteria epatica comune
Ligamento epatico-duodenale
Asse celiaco
Linfonodi paraortici sinistri *
Linfonodi retroaortici *
Subpilorici (soltanto se N+)

*** N infradiaframmatici**

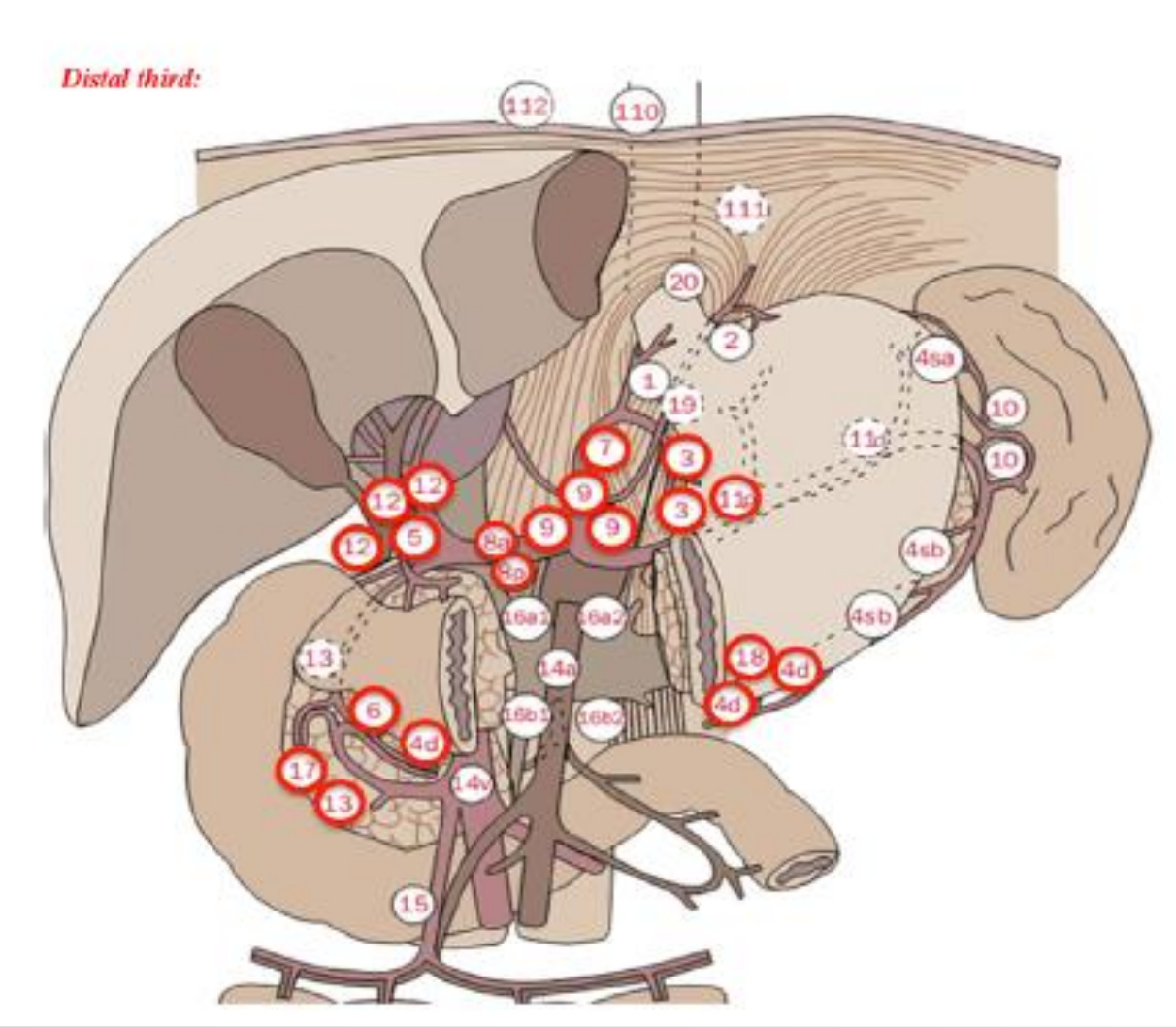
TUMORE DEL 1/3 MEDIO : N



Cardiali
Piccola e grande curvatura
Antro e Piloro
Arteria splenica ed ilo splenico
Catena retropancreatica superiore
Linfonodi posteriori alla testa del pancreas
Arteria epatica comune
Ligamento epatico-duodenale
Asse celiaco
Linfonodi paraortici sinistri *
Linfonodi retroaortici *
Subpilorici

*** N infradiaframmatici**

TUMORE DEL 1/3 DISTALE : N



Sub pilorici
Linfonodi perigastrici:
Cardiali,
Piccola e grande curvatura
Antro e piloro
Arteria epatica comune
Asse celiaco
Ilo splenico (soltanto se N+)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

Adjuvant radiotherapy for gastric cancer—end of the road?

57,9%

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Adjuvant chemotherapy is superior to chemoradiation after D2 surgery for gastric cancer in the per-protocol analysis of the randomized CRITICS trial

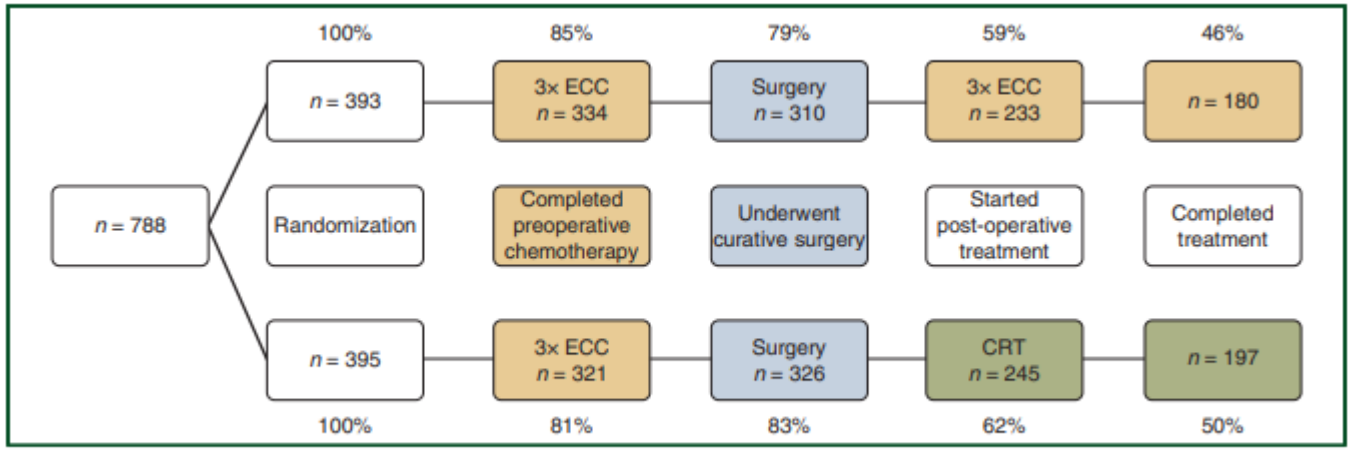


Figure 1. Study profile.
CRT, chemoradiotherapy 45 Gy/25 fractions + capecitabine + cisplatin; ECC, epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC).

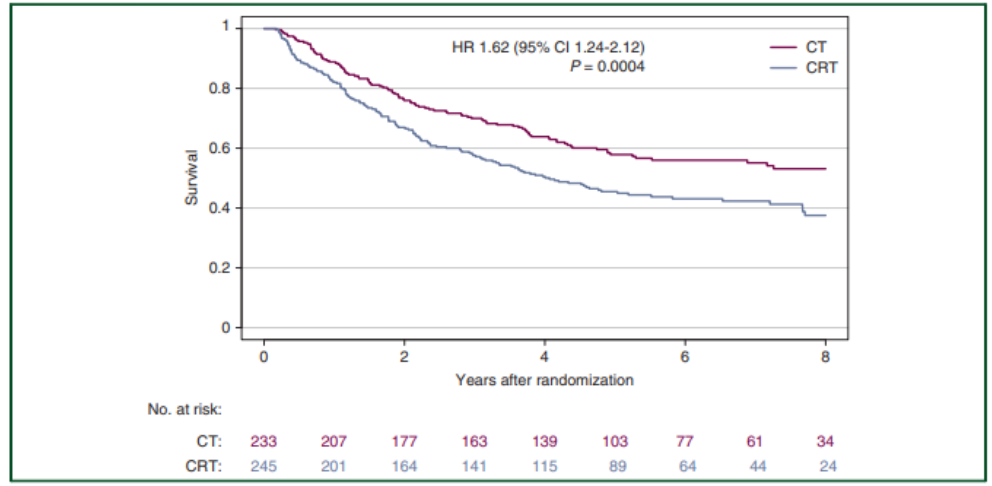


Figure 3. Kaplan–Meier curve overall survival for the chemotherapy and chemoradiotherapy group (per-protocol).
CI, confidence interval; CRT, chemoradiotherapy; CT, chemotherapy; HR, hazard ratio.

45,5%

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

EDITORIAL

Adjuvant radiotherapy for gastric cancer—end of the road?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

A randomized phase III trial comparing adjuvant single-agent S1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial☆

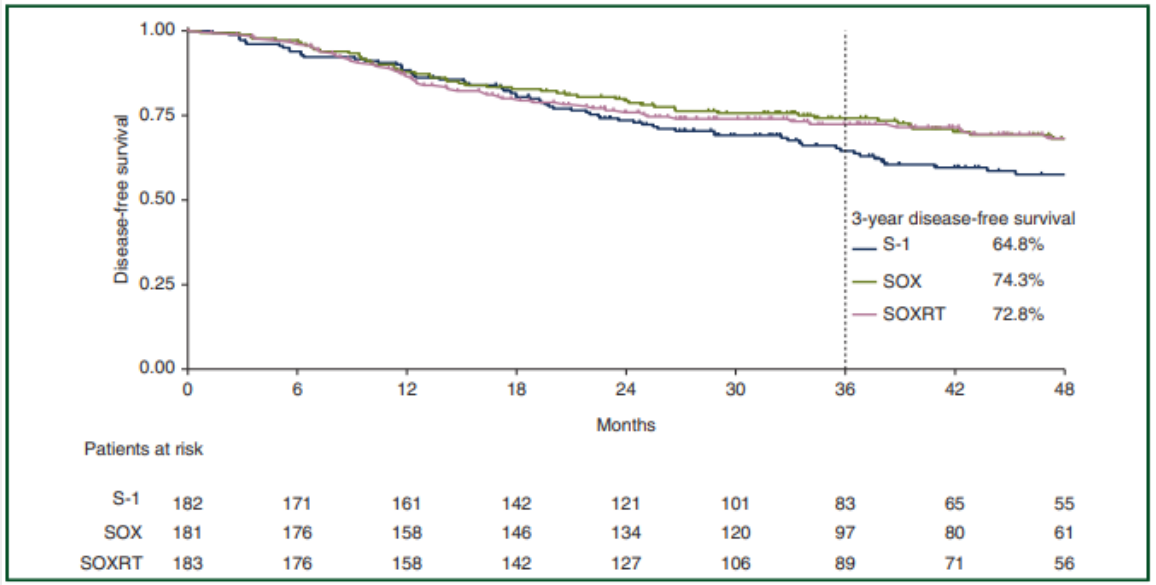
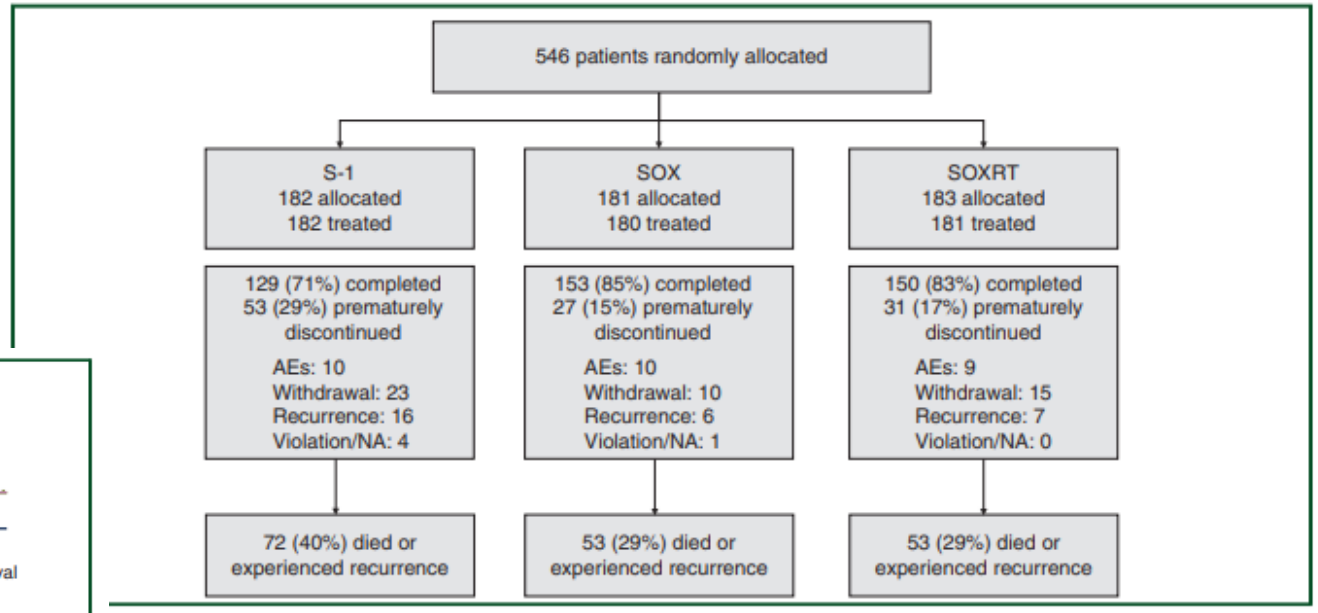


Figure 2. Treatment outcome in terms of disease-free survival in three arms for the Adjuvant chemoRadioTherapy In Stomach Tumors (ARTIST) II trial.
S-1, monotherapy; SOX, S-1 plus oxaliplatin; SOXRT, SOX plus chemoradiotherapy.



e CONSORT diagram for the Adjuvant chemoRadioTherapy In Stomach Tumors (ARTIST) II trial.
event; S-1, monotherapy; SOX, S-1 plus oxaliplatin; SOXRT, SOX plus chemoradiotherapy.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY

EDITORIAL

CRT PREOPERATORIA

...the road?

Slagter et al. BMC Cancer (2018) 18:877
https://doi.org/10.1186/s12885-018-4770-2

BMC Cancer

STUDY PROTOCOL Open Access

CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer

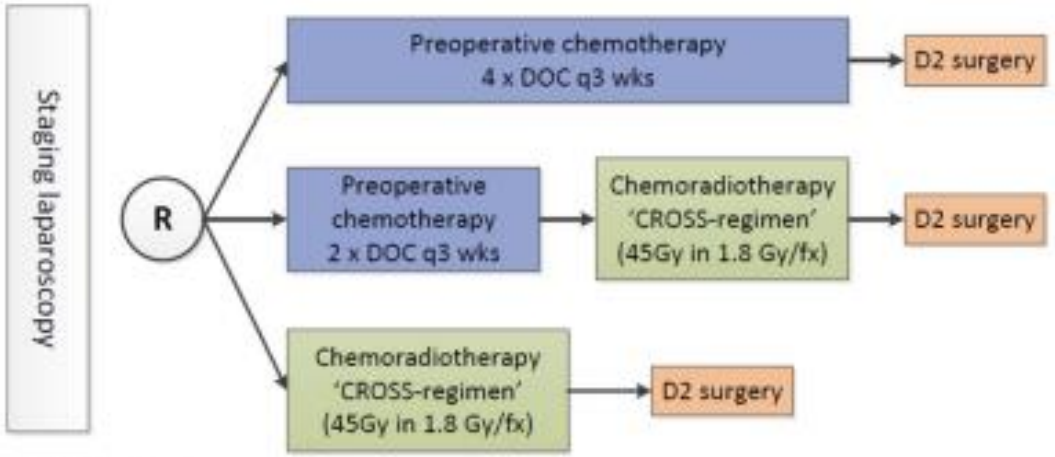


Fig. 1 Randomisation scheme CRITICS-II trial

Leong et al. BMC Cancer (2015) 15:532
DOI 10.1186/s12885-015-1529-x

BMC Cancer

STUDY PROTOCOL Open Access

TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG)

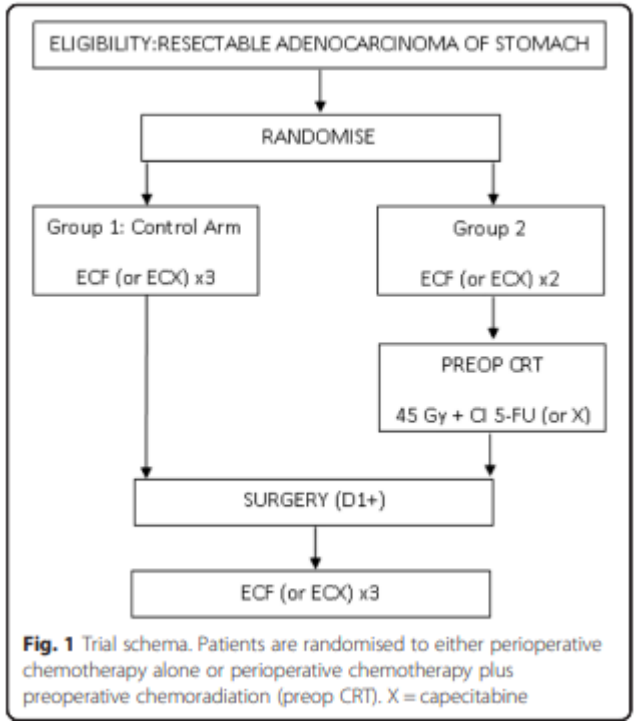


Fig. 1 Trial schema. Patients are randomised to either perioperative chemotherapy alone or perioperative chemotherapy plus preoperative chemoradiation (preop CRT). X = capecitabine

CHEMIORADIOTERAPIA PREOPERATORIA

VANTAGGI

- Migliore resecabilità successiva
- Minore rischio di disseminazione intraoperatoria
- Tumore mai trattato e quindi biologicamente più sensibile
- Tumore più ossigenato
- **Intestino ed organi ipocondriaci più mobili rispetto al postoperatorio, con minori possibilità di danni da radiazioni**

SVANTAGGI

- Differimento dell'intervento chirurgico, con rischio di progressione precoce

Chemioradioterapia preoperatoria quale ruolo nella pratica clinica?

Non esiste un ruolo preciso nella pratica clinica ,
La sua applicazione è legata a studi clinici

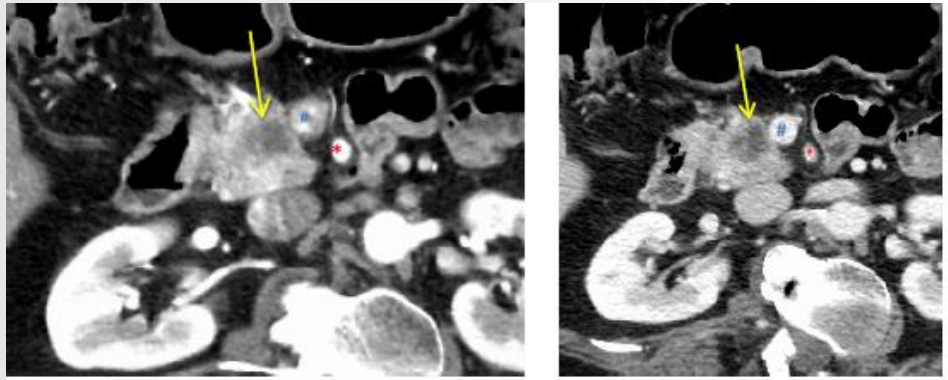
POST-OP

- Bassa compliance
- Anatomia critica
- Schema CT (5FU ic) “obsoleto”
- Terapia di supporto protratta a lungo

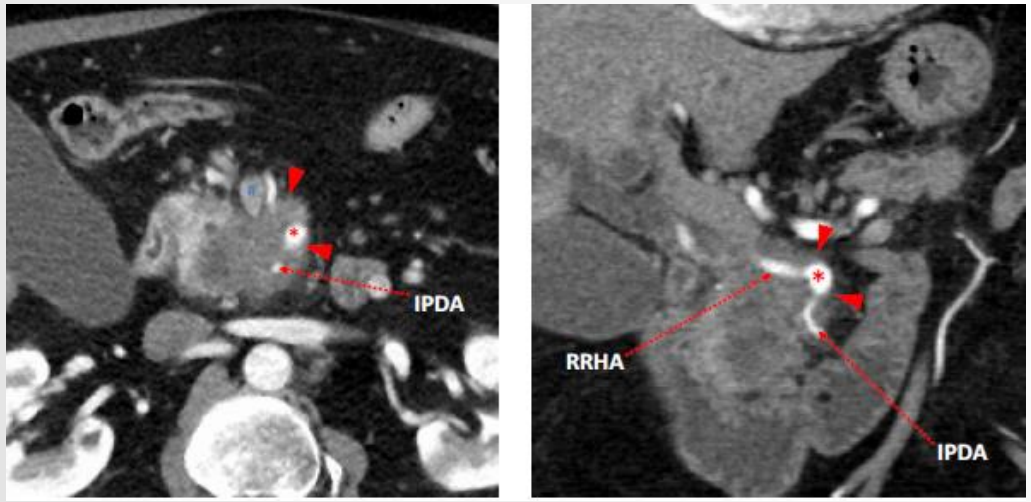
PRE-OP

- Alta compliance
- Elevata tossicità acuta
- Nuovi schemi di CT
- Terapia di supporto precoce

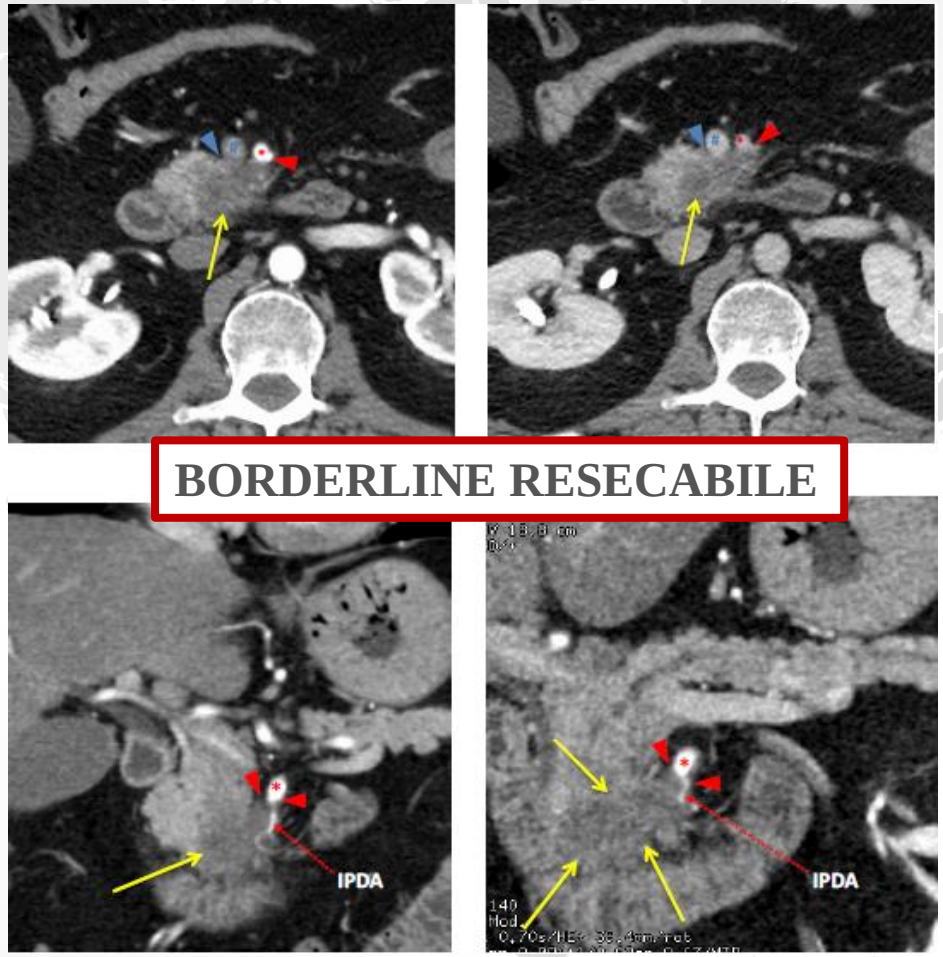
PANCREAS



solo nel 20% dei casi **RESECABILE**



NON RESECABILE



BORDERLINE RESECABILE

30% dei casi localmente avanzata non resecabile

Malattia borderline resecabile

PIANIFICATA CHIRURGIA UPFRONT SENZA TRATTAMENTO NEOADIUVANTE

- NEOPLASIA G1-G2
- Ca19.9 < 200 U/mL
- Paziente è paucisintomatico
- Eventuale resezione vascolare venosa limitata

Malattia borderline resecabile

PIANIFICATA CHIRURGIA DOPO TRATTAMENTO NEOADIUVANTE

Elevato rischio di resezione non radicale e di recidiva precoce dopo chirurgia

Neoadjuvant therapy for patients with borderline resectable pancreatic cancer: A systematic review and meta-analysis of response and resection percentages

Volume 16, Issue 1, January–February 2016, Pages 28-37

Neoadjuvant Therapy for Pancreatic Cancer: Systematic Review of Postoperative Morbidity, Mortality, and Complications

Volume 39 , Issue 3, June 2016 , Pages 302–313

Quanto è importante il controllo locale in una malattia “sistemica” sin dall’inizio?

***DPC4* Gene Status of the Primary Carcinoma Correlates With Patterns of Failure in Patients With Pancreatic Cancer**

Christine A. Iacobuzio-Donahue, Baojin Fu, Shinichi Yachida, Mingde Luo, Hisashi Abe, Clark M. Henderson, Felip Vilardell, Zheng Wang, Jesse W. Keller, Priya Banerjee, Joseph M. Herman, John L. Cameron, Charles J. Yeo, *Marc K. Halushka, James R. Eshleman, Marian Raben, Alison P. Klein, Ralph H. Hruban, Manuel Hidalgo, and Daniel Laheru*

- Circa il 30% dei pazienti muore per “ locally destructive disease” con o senza metastasi a distanza.
- C’è una popolazione con “genetically determined tendency” alla progressione locale

La percentuale di **ripresa locale** è elevata : sino al 50% nei pazienti sottoposti a chirurgia esclusiva

Abrams RA, Lowy AM et al. Combined modality tretment of resectable and borderline resectable pancreas cancer: expert consensus statement. Ann Surg Oncol; 2009; 16(7): 1751-1756.

RADIOTERAPIA

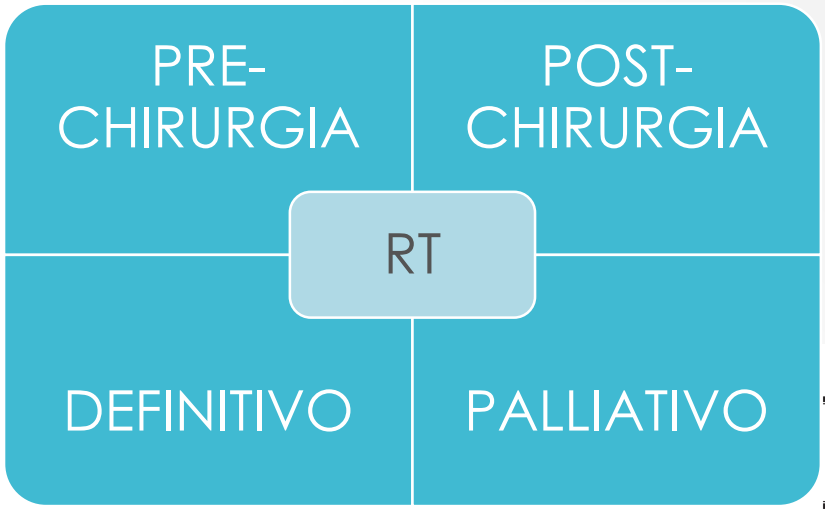
Key question 1:
Indications for conventionally fractionated RT or SBRT

- ❑ adjuvant therapy?
- ❑ neoadjuvant therapy?
- ❑ definitive therapy?

Table 2 Recommendations for indications for conventionally fractionated RT or SBRT

KQ 1 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. Following surgical resection of pancreatic cancer, adjuvant conventionally fractionated RT with chemotherapy in select high-risk patients is conditionally recommended.	Conditional	Low	92% *
Implementation Remark: High-risk clinical features would include positive lymph nodes and margins regardless of tumor location within the pancreas.			
2. Following surgical resection of pancreatic cancer, adjuvant SBRT is only recommended on a clinical trial or multi-institutional registry.	Strong	Very low	100% *
3. For patients with resectable pancreatic cancer, neoadjuvant therapy is conditionally recommended.	Conditional	Low	92% *
4. For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by conventionally fractionated RT with chemotherapy is conditionally recommended.	Conditional	Moderate	85% *
5. For patients with borderline resectable pancreatic cancer and select locally advanced pancreatic cancer appropriate for downstaging prior to surgery, a neoadjuvant therapy regimen of systemic chemotherapy followed by multifraction SBRT is conditionally recommended.	Conditional	Low	77% *
6. For patients with locally advanced pancreatic cancer not appropriate for downstaging to eventual surgery, a definitive therapy regimen of systemic chemotherapy followed by either (1) conventionally fractionated RT with chemotherapy, (2) dose-escalated chemoradiation, or (3) multifraction SBRT without chemotherapy is conditionally recommended.	Conditional	Low	85% *

Abbreviations: KQ = key question; RT = radiation therapy; SBRT = stereotactic body radiation therapy.
* The medical physics representative abstained from rating these recommendations.



practical radiation oncology
pro
www.practicalradonc.org

ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a,*], Devon Godfrey PhD [a], Karyn A. Goodman MD [b],

ASPETTI TECNICI

RADIOTERAPIA CONVENZIONALE

RADIOTERAPIA STEREOTASSICA

EFFETTI COLLATERALI

Malattia resecabile → setting : adiuvante

radicalità della resezione chirurgica R1/R2

lo stadio linfonodale (pN+);

PRINCIPALI FATTORI PROGNOSTICI

- Negli studi più recenti è stato definito il parametro "Lymph node ratio" (LNR), ovvero il rapporto fra il numero di linfonodi positivi e il numero totale di linfonodi reperiti, permettendo quindi di tener conto sia dell'estensione di malattia, che dell'adeguatezza della linfadenectomia.

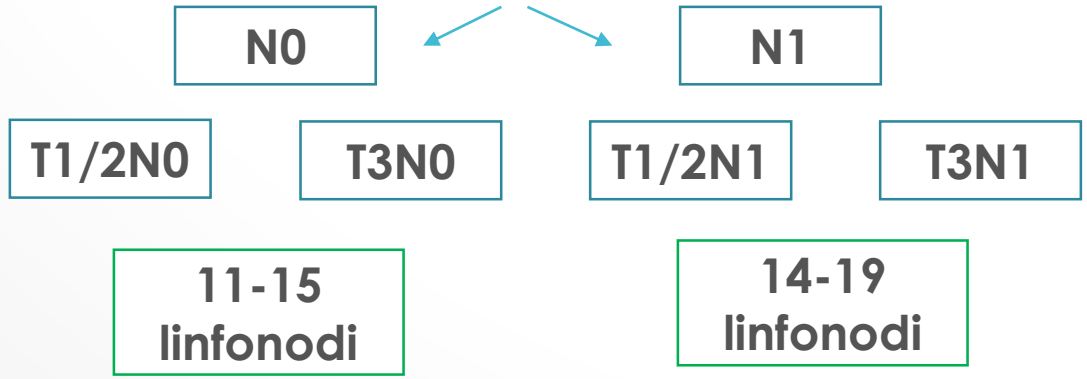
- In tutte le neoplasie del tratto gastroenterico, incluso il pancreas, il LNR assume un ruolo prognostico indipendente nella categoria di pazienti pN+, permettendo quindi di considerare nei pazienti con positività linfonodale il ruolo dell'adeguatezza chirurgica in termini di staging linfonodale.

Numero di linfonodi negativi

P< 0,0001

Numero totale di linfonodi asportati

COORTE : 20631 pazienti



September 2006, Volume 13, Issue 9, pp 1189–1200

Extent of Lymph Node Retrieval and Pancreatic Cancer Survival: Information from a Large US Population Database

Malattia resecabile → setting : neo-adiuvante

Parametri associati a mortalità precoce dopo chirurgia
(G3, infiltrazione arteria splenica, Ca 19.9 elevato, LNR +)

→ **TERAPIA NEOADIUVANTE**

L' IMPORTANZA DEL FATTORE PROGNOSTICO Ca 19.9

Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer.
Kondo N1, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Nakashima A, Sakabe R, Shigemoto N, Kato Y, Ohge H, Sueda T.

Preoperative CA 19-9 level is an important prognostic factor in patients with pancreatic adenocarcinoma treated with surgical resection and adjuvant concurrent chemoradiotherapy.
Hallemeier CL1, Botros M, Corsini MM, Haddock MG, Gunderson LL, Miller RC.

CA 19-9 level as indicator of early distant metastasis and therapeutic selection in resected pancreatic cancer.
Kim TH, Han SS, Park SJ, Lee WJ, Woo SM, Yoo T, Moon SH, Kim SH, Hong EK, Kim DY, Park JW.

High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer.
Alexakis N, Gomatos IP, Sbarounis S, Toutouzas K, Katsaragakis S, Zografos G, Konstandoulakis MM.

Malattia resecabile → setting : neo-adiuvante

Parametri associati a mortalità precoce dopo chirurgia
(G3, infiltrazione arteria splenica, Ca 19.9 elevato, LNR +)

→ **TERAPIA NEOADIUVANTE**


Radiotherapy and Oncology 143 (2020) 101–107

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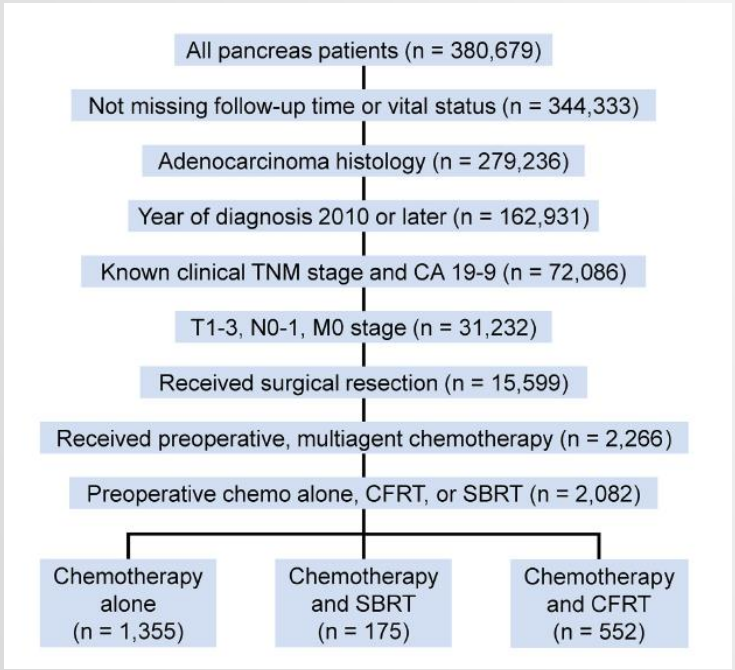
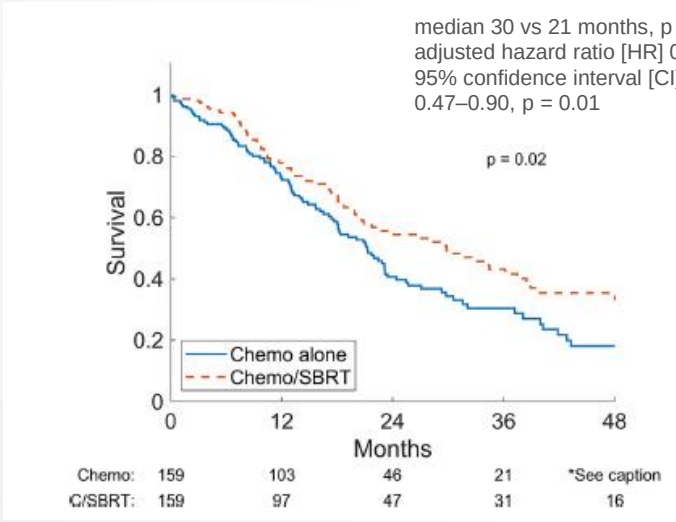
Original Article

Neoadjuvant treatment strategies for resectable pancreas cancer: A propensity-matched analysis of the National Cancer Database

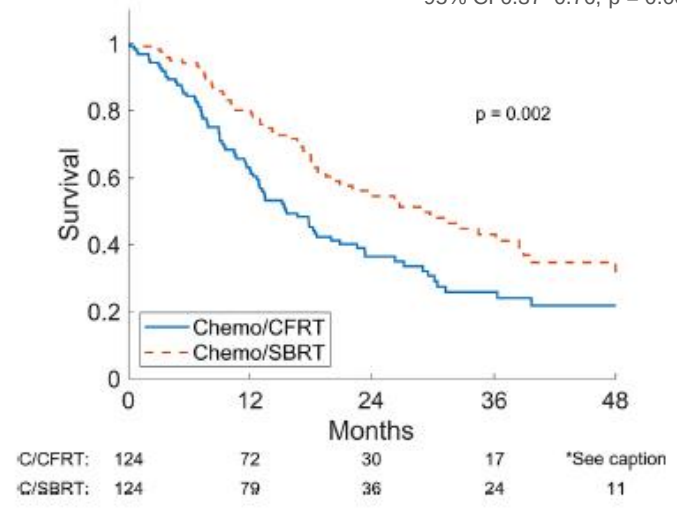
Michael Xiang [a,b], Gregory M. Heestand [c], Daniel T. Chang [a,*], Erqi L. Pollom [a,b,*]



median 30 vs 21 months, p = 0.02;
adjusted hazard ratio [HR] 0.65,
95% confidence interval [CI]
0.47–0.90, p = 0.01



median 29 vs 16 months, p = 0.002;
adjusted HR 0.53,
95% CI 0.37–0.76, p = 0.001



- pCR CT 2.2%
- pCR CT + CFRT 4.9%
- pCR CT + SBRT 6.1%

(p = 0.002).

- R0 CT 81%
- R0 CT + CFRT 86%
- R0 CT + SBRT 91%

(p < 0.0001),

LA **CHIRURGIA** RAPPRESENTA LA PROSPETTIVA DI CURA , MA LA RESEZIONE CON INTENTO RADICALE PUÒ ESSERE ESEGUITA **SOLO NEL 25% DEI CASI**

BORDERLINE RESECABILE

NON RESECABILE

CT

CT + RADIOTERAPIA

Katz et al. BMC Cancer (2017) 17:505
DOI 10.1186/s12885-017-3441-z

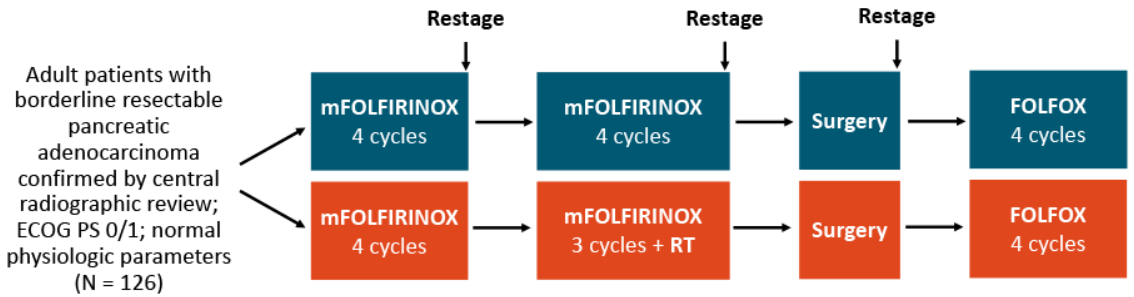
BMC Cancer

STUDY PROTOCOL Open Access

Alliance for clinical trials in oncology (ALLIANCE) trial A021501: preoperative extended chemotherapy vs. chemotherapy plus hypofractionated radiation therapy for borderline resectable adenocarcinoma of the head of the pancreas

Matthew H. G. Katz[1*], Fang-Shu Ou[2], Joseph M. Herman[1], Syed A. Ahmad[3], Brian Wolpin[4], Robert Marsh[5]

- Multicenter, randomized phase II trial



- Primary endpoint: binary 18-mo OS rate
- Key secondary endpoints: EFS, safety, R0 resection rate, pCR rate

RT

SBRT (6.6 Gy × 5) o HIGRT (5 Gy × 5).

Meeting Abstract | 2021 Gastrointestinal Cancers Symposium

PANCREATIC CANCER

Alliance A021501: Preoperative mFOLFIRINOX or mFOLFIRINOX plus hypofractionated radiation therapy (RT) for borderline resectable (BR) adenocarcinoma of the pancreas.

BORDERLINE RESECABILE

Therapy by treatment arm (N = 126), (n [%]).

	Arm A (mFOLFIRINOX) n = 70	Arm B (mFOLFIRINOX + RT) n = 56
Initiated preop treatment	66	55
Started cycle 8 ctx or RT*	47 (71)	40 (73)
Surgery	38 (58)	28 (51)
Pancreatectomy	32 (48)	19 (35)
R0 pancreatectomy	28 (42)	14 (25)
Initiated postop ctx	22 (33)	13 (24)
Completed all treatment	20 (30)	10 (18)

Ctx, chemotherapy

*SBRT (n = 35); HIGRT (n = 5)

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DOSE

	mFOLFIRINOX (n = 65)	mFOLFIRINOX + RT (n = 55)
OS		
▪ Events	35	40
▪ Median OS, mos (95% CI)	29.8 (21.1-NE)	17.1 (12.8-24.4)
▪ 18-mo OS rate, %	66.4	47.3
EFS		
▪ Events	45	44
▪ Median EFS, mos (95% CI)	15.0 (11.2-21.9)	10.2 (6.7-17.3)

Preoperative Treatment-Related AEs

AE, n (%)	mFOLFIRINOX (n = 65)	mFOLFIRINOX + RT (n = 55)
Experienced ≥ 1 grade 3+ AE	37 (57)	35 (64)
▪ During mFOLFIRINOX	37 (57)	35 (64)
▪ During RT (n = 40)	-	5 (13)
Experienced ≥ 1 grade 4+ AE	11 (17)*	5 (9)
▪ During mFOLFIRINOX	11 (17)	5 (9)
▪ During RT (n = 40)	-	0

*1 patient experienced a grade 5 event (sepsis).

Surgical AEs

AE, n (%)	mFOLFIRINOX (n = 32)	mFOLFIRINOX + RT (n = 19)
Weight loss (grade 3+)	3 (11)	1 (8)
Anemia (grade 3+)	1 (4)	2 (17)
Pancreatic fistula or intra-abdominal abscess	3 (9)	3 (16)
Wound infection	2 (6)	3 (16)
Readmission	5 (16)	8 (42)
Reoperation	4 (13)	1 (5)
Death	1 (3)	2 (11)

Malattia Localmente Avanzata

NON RESECABILE

PS ECOG < 2

- CT INDUZIONE → CRT → ?CHIRURGIA

PS ECOG > 2

- MONOCHEMIOTERAPIA vs BSC

Malattia Localmente Avanzata

NON RESECABILE

Practical Radiation Oncology® (2020) 10, e495–e507

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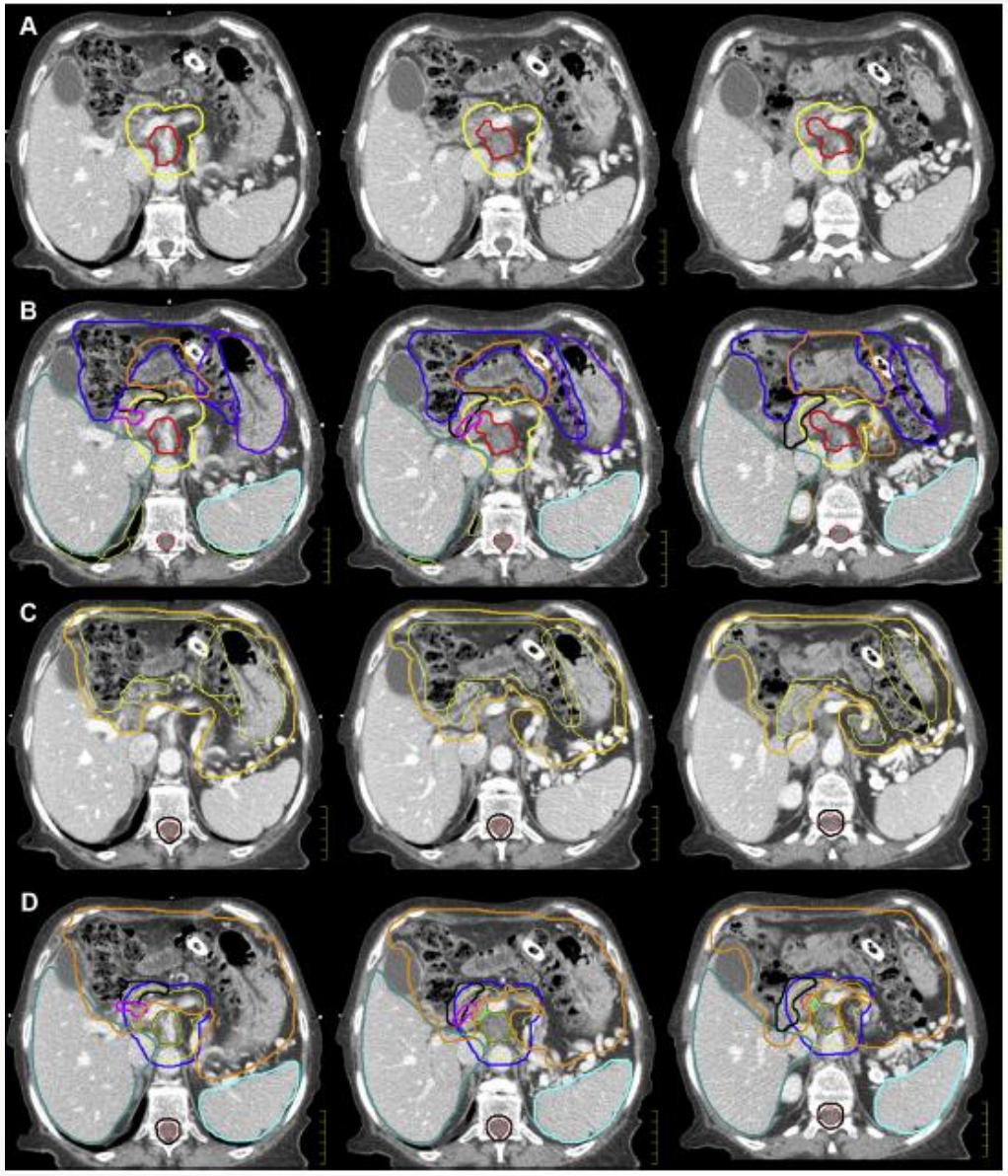
Clinical Investigation

Dose-Escalated Radiation Therapy for Pancreatic Cancer: A Simultaneous Integrated Boost Approach

Eugene J. Koay, MD, PhD,[a,*,1] Alexander N. Hanania, MD, MPH,[b,1]
William A. Hall, MD,[c] Cullen M. Taniguchi, MD, PhD,[a]
Neal Rebueno, CMD,[a] Sten Myrehaug, MD,[d] Katharine L. Aitken, MD,[e]
Laura A. Dawson, MD,[f] Christopher H. Crane, MD,[g]
Joseph M. Herman, MD,[a] and Beth Erickson, MD[c]



Case 1: 15-Fraction Hypofractionated IMRT With SIB

PTV_Low is intended to comprehensively cover the tumor with margin and areas of possible microscopic extension and elective nodal basins; therefore, the dose will be lower to this volume **(3750 cGy/15 fx)** with a uniform, unmodified, 5-mm expansion.

Meanwhile, a high-dose planning structure, **zPTV_High**, will encompass the planning volume for dose escalation **(6750 cGy/15 fx).**

Malattia Localmente Avanzata

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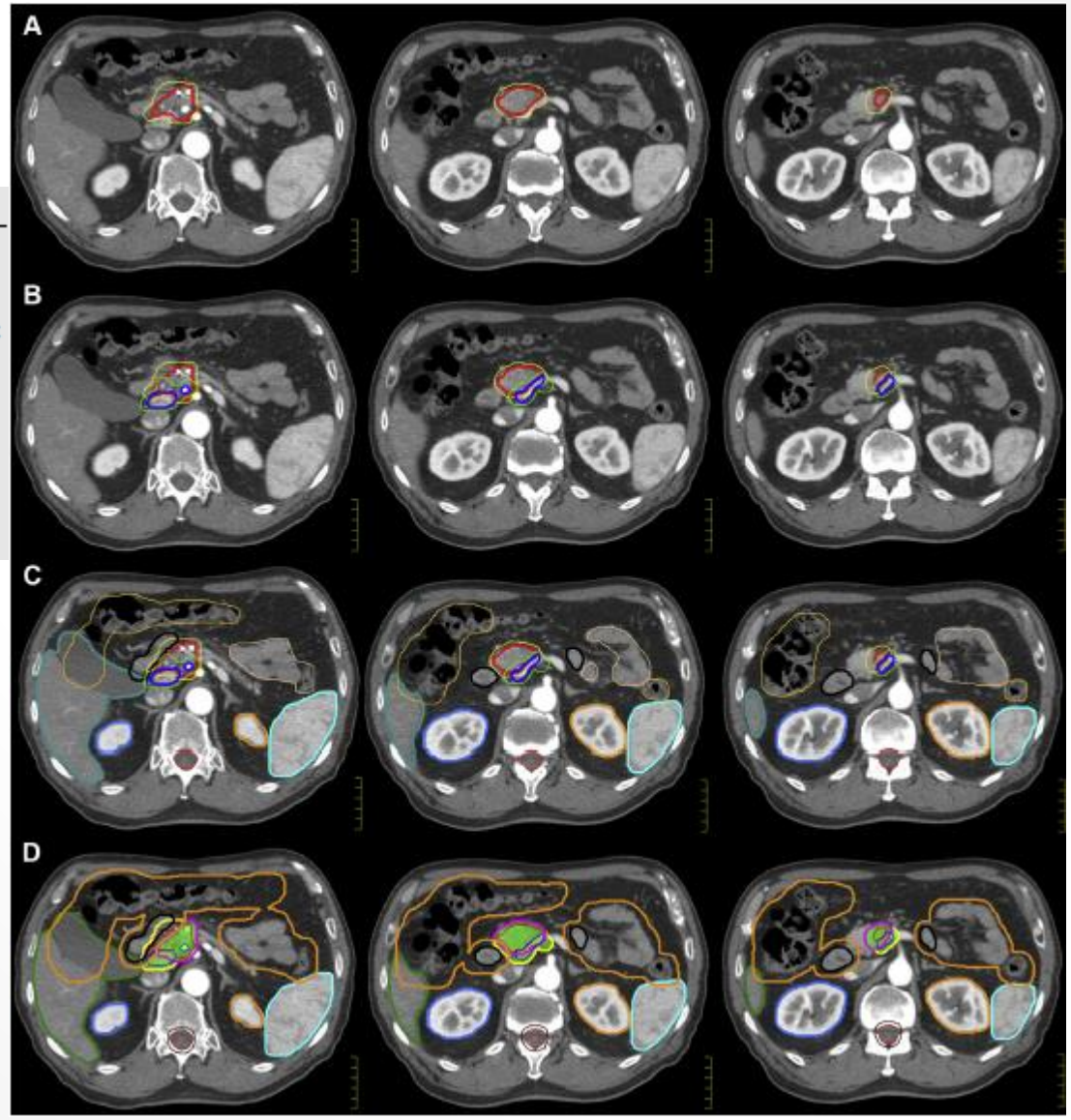
Table 2 SBRT selection criteria for dose escalation

Suggested SBRT (5 Fractions) dose-escalation inclusion criteria
Cytologic- and biopsy-confirmed adenocarcinoma
Locally advanced, unresectable, or borderline (abutment of SMA, celiac axis, SMV, or PV involvement*)
ECOG ≤2
Pancreatic tumor size ≤5 cm
No regional adenopathy†
No evidence of distant metastasis
Metal stent in place if duodenal stent required
Reproducible motion management (encompass tumor motion ≤5 mm)

NON RESECABILE

Case 2: 5-Fraction SBRT

PTV_Low represents the low-dose level (**3300 cGy**) and encompasses a 3-mm expansion of both the iGTV and TVI to ensure the minimum dose encompasses these structures without regard to normal structures. **zPTV_High**, is created from (iGTV þ TVI) þ 3 mm with the GI PRV subtracted; in essence, this is the PTV_Low modified by the luminal OARs and will represent the targeted area for maximum dose **(5000 cGy)** to the tumor and TVI



Malattia Localmente Avanzata

NON RESECABILE

Practical Radiation Oncology® (2020) 10, e495–e507

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Clinical Investigation

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Joseph M. Herman, MD,[a] and Beth Erickson, MD[c]

Table 1 Dosimetric objectives and constraints

5-Fraction SBRT dose escalation		
	PTV_Low	zPTV_High*
Target	([iGTV + TVI] + 3 mm)	([iGTV + TVI] + 3 mm)−GI PRV
Total dose, cGy	3300	5000
Objective	>98% coverage	1. ≥98% coverage of iGTV to 4000 cGy 2. ≥95% coverage of TVI to 4000 cGy 3. ≥90%-95% coverage of iGTV to 5000 cGy†
15-Fraction IMRT dose escalation		
	PTV_Low	zPTV_High*
Target	(iGTV + CA/SMA‡) + 10 mm	iGTV−GI PRV
Expansion	CTV + 5 mm	None
Total dose	3750 cGy	6750 cGy
Objective	>98% coverage	1. ≥98% coverage of iGTV to 4500 cGy 2. ≥90%-95% coverage of iGTV to 6750 cGy†
Organ at Risk	15-fraction (IMRT) constraint	5-fraction (SBRT) constraint
Spinal cord	Dmax <30 Gy	V20 <1 cm^3
Liver	700 cm^3 <24 Gy Mean <24 Gy	V12 <50%
Kidneys (left and right)	V20 <33%	V12 <75%
iStomach	Dmax < 45 Gy	V40 <0.5 cm^3 V35 <1 cm^3 V30 <2 cm^3
iDuodenum	Dmax <45 Gy	V40 <0.5 cm^3 V35 <1 cm^3 V30 <3 cm^3
iBowel (small)	Dmax <45 Gy	V40 <0.5 cm^3 V35 <1 cm^3 V30 <2 cm^3
iBowel (large)	Dmax <50 Gy	V35 <1 cm^3
Bile duct	Dmax <70 Gy	Max 55 Gy
Spleen	Mean <6 Gy	Mean <2 Gy
Heart	V40 < 10%, V50 <1 cm^3, Max 55 Gy	Max 30 Gy

Key question 2: Dose fractionation and target volumes

- ❑ conventionally fractionated RT and chemotherapy?
- ❑ SBRT?

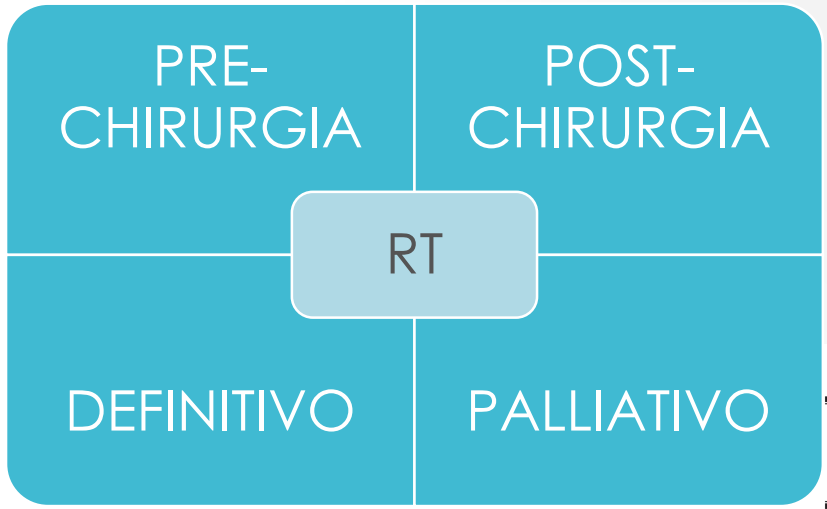
8. For patients with borderline resectable pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.	Strong	High	92%†
Implementation Remark: SBRT does not routinely treat elective nodes.			
9. For patients with locally advanced pancreatic cancer selected for SBRT, a treatment volume including the gross tumor volume with a small margin is recommended.	Strong	High	100%†

Key question 3: Sequencing of chemotherapy and RT

- ❑ adjuvant therapy?
- ❑ neoadjuvant therapy?
- ❑ definitive therapy?

Table 4 Recommendations for sequencing of chemotherapy and RT in patients receiving RT

KQ 3 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with resected pancreatic cancer receiving adjuvant therapy, delivery of chemoradiation following 4-6 months of systemic chemotherapy is recommended.	Strong	Moderate	92%*
2. For patients with borderline resectable pancreatic cancer receiving neoadjuvant therapy, delivery of RT following 2-6 months of systemic chemotherapy is recommended.	Strong	Moderate	92%*
3. For patients with unresectable or locally advanced pancreatic cancer without systemic progressionfollowing 4-6+ months of chemotherapy, definitive RT is recommended.	Strong	Moderate	85%*



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ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a,*], Devon Godfrey PhD [a], Karyn A. Goodman MD [b],

ASPETTI TECNICI

EFFETTI COLLATERALI

Key question 4: Simulation considerations

- ☒ motion management
- ☒ image guidance
- ☒ contrast administration during computed Tomography (CT) simulation

4. For patients receiving conventionally fractionated RT for pancreatic cancer, daily image guidance is recommended. Implementation Remarks: • Bony anatomy and surgical stents are each poor surrogates for pancreas target positioning; if used for image guidance, large internal target volume margins are necessary. • Where possible, the cine (fluoroscopic) imaging is useful, in addition to 2-D or 3-D image guidance, to confirm that the ITV adequately accounts for respiratory motion variations or intra–breath-hold drift.	**Strong**	**Moderate**	**100%***
5. For patients receiving SBRT for pancreatic cancer, daily image guidance with fiducial markers and volumetric imaging is recommended. Implementation Remarks: • Bony anatomy and surgical stents are each poor surrogates for pancreas target positioning; if used for image guidance, large internal target volume margins are necessary. • Where possible, the use of cine (fluoroscopic) imaging is suggested, in addition to 2-D or 3-D image guidance, to confirm that the ITV adequately accounts for respiratory motion variations or intra–breath-hold drift.	**Strong**	**Moderate**	**100%***
6. Unless there is a contraindication to IV contrast, patients with pancreatic cancer treated with RT should receive IV contrast at CT simulation; multiphasic CT with a high contrast flow rate and injection volume and patient-specific scan timing is	**Strong**	**High**	**100%***

Key question 5: Treatment planning techniques

Table 6 Recommendation for treatment planning

KQ 5 recommendation	Strength of recommendation	Quality of evidence	Consensus
1. For treatment of localized pancreatic cancer, modulated treatment techniques such as IMRT and VMAT for planning and delivery of both conventionally fractionated and hypofractionated RT are recommended.	**Strong**	**Moderate**	**100%***

Abbreviations: IMRT = intensity modulated radiation therapy; KQ = key question; RT = radiation therapy; VMAT = volumetric-modulated arc therapy.

IMRT/VMAT

ASPETTI TECNICI

PRE-CHIRURGIA | POST-CHIRURGIA

RT

DEFINITIVO | PALLIATIVO

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ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a,*], Devon Godfrey PhD [a], Karyn A. Goodman MD [b],

RADIOTERAPIA CONVENZIONALE | RADIOTERAPIA STEREOTASSICA

EFFETTI COLLATERALI

Practical Radiation Oncology (2017) 7, e489-e497

www.practicalradonc.org

Basic Original Report

Triphasic contrast enhanced CT simulation with bolus tracking for pancreas SBRT target delineation

Devon J. Godfrey PhD [a,*], Bhavik N. Patel MD, MBA [b], Justus D. Adamson PhD [a], Ergys Subashi PhD [a], Joseph K. Salama MD [a], Manisha Palta MD [a]

[a]Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina
[b]Department of Radiology, Duke University Medical Center, Durham, North Carolina

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Abstract

Purpose: Bolus-tracked multiphasic contrast computed tomography (CT) is often used in diagnostic radiology to enhance the visibility of pancreas tumors, but is uncommon in radiation therapy pancreas CT simulation, and its impact on gross tumor volume (GTV) delineation is unknown. This study evaluates the lesion conspicuity and consistency of pancreas stereotactic body radiation therapy (SBRT) GTVs contoured in the different contrast phases of triphasic CT simulation scans.

Methods and materials: Triphasic, bolus-tracked planning CT simulation scans of 10 consecutive pancreas SBRT patients were acquired, yielding images of the pancreas during the late arterial (LA), portal venous (PV), and either the early arterial or delayed phase. GTVs were contoured on each phase by a gastrointestinal-specialized radiation oncologist and reviewed by a fellowship-trained abdominal radiologist who specializes in pancreatic imaging. The volumes of the registered GTVs, their overlap

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ORIGINAL RESEARCH

WILEY Cancer Medicine

Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer

Soumon Rudra[1] | Naomi Jiang[2] | Stephen A. Rosenberg[3] | Jeffrey R. Olsen[1] | Michael C. Roach[1] | Leping Wan[1] | Lorraine Portelance[4] | Eric A. Mellon[4] | Anna Bruynzeel[5] | Frank Lagerwaard[5] | Michael F. Bassetti[3] | Parag J. Parikh[1] | Percy P. Lee[2]

[1]Department of Radiation Oncology, Washington University School of Medicine, St. Louis, Missouri
[2]Department of Radiation Oncology, David Geffen School of Medicine at UCLA, Los Angeles, California
[3]Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Carbone Cancer Center, Madison, Wisconsin
[4]Department of Radiation Oncology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida
[5]Department of Radiation Oncology, VU University Medical Center, Amsterdam, Netherlands

Correspondence
Parag J. Parikh, Department of Radiation Oncology, Henry Ford Cancer Institute, Detroit, MI.
Email: pparikh2@hfhs.org

Present address
Stephen A. Rosenberg, Department of Radiation Oncology, Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, Florida 33612
Jeffrey R. Olsen, Department of Radiation Oncology, University of Colorado, 1665 Aurora Court, Suite 1032, Aurora, Colorado 80045
Parag J. Parikh, Department of Radiation Oncology, Henry Ford Cancer Institute, 2799 West Grand Blvd, Detroit, Michigan 48202

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Abstract

Background: Adaptive magnetic resonance imaging-guided radiation therapy (MRgRT) can escalate dose to tumors while minimizing dose to normal tissue. We evaluated outcomes of inoperable pancreatic cancer patients treated using MRgRT with and without dose escalation.

Methods: We reviewed 44 patients with inoperable pancreatic cancer treated with MRgRT. Treatments included conventional fractionation, hypofractionation, and stereotactic body radiation therapy. Patients were stratified into high-dose (biologically effective dose [BED_{10}] >70) and standard-dose groups ($BED_{10} \leq 70$). Overall survival (OS), freedom from local failure (FFLF) and freedom from distant failure (FFDF) were evaluated using Kaplan-Meier method. Cox regression was performed to identify predictors of OS. Acute gastrointestinal (GI) toxicity was assessed for 6 weeks after completion of RT.

Results: Median follow-up was 17 months. High-dose patients (n = 24, 55%) had statistically significant improvement in 2-year OS (49% vs 30%, $P = 0.03$) and

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Basic Original Report

Australasian Gastrointestinal Trials Group (AGITG) and Trans-Tasman Radiation Oncology Group (TROG) Guidelines for Pancreatic Stereotactic Body Radiation Therapy (SBRT)

Andrew Oar, MBBS, MIPH, FRANZCR,[a,b,*] Mark Lee, MBBS, MSc, FRANZCR,[a] Hien Le, MBBS, FRANZCR,[c] George Hruby, BHB, MBChB, FRANZCR,[d,e] Raymond Dalfsen, BMRSc,[c] David Pryor, MBBS, FRANZCR,[f] Dominique Lee, MBChB, FRANZCR,[f] Julie Chu, MBBS, FRANZCR,[g] Lois Holloway, PhD,[b,h,i,j] Adam Briggs, MSc,[d] Andrew Barbour, PhD, FRACS,[f,k] Sarat Chander, MBBS, FRANZCR,[g] Sweet Ping Ng, MBBS, FRANZCR,[g] Jas Samra, D Phil, FRACS,[d,e] John Shakeshaft, MA, PhD,[a] David Goldstein, MBBS, FRACP,[l,m] Nam Nguyen, MBBS, PhD, FRACP,[n] Karyn A. Goodman, MD, MS,[o] Daniel T. Chang, MD,[p] and Andrew Kneebone, MBBS, FRANZCR[d,e]

[a]Icon Cancer Centre, Gold Coast University Hospital, Gold Coast; [b]Liverpool and Macarthur Cancer Therapy Centres, Sydney, Australia; [c]Department of Radiation Oncology, Royal Adelaide Hospital, Adelaide, Australia; [d]Royal North Shore Hospital, Sydney, Australia; [e]University of Sydney, Sydney, Australia; [f]Princess Alexandra Hospital, Brisbane, Australia; [g]Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia; [h]South Western Clinical School, University of New South Wales, Sydney, Australia; [i]Institute of Medical Physics, University of Sydney, Sydney, Australia; [j]Centre for Medical Radiation Physics, University of Wollongong, Wollongong, Australia; [k]University of Queensland, Diamantina Institute, Translational Research Institute, Woolloongabba, Australia; [l]Department of Medical Oncology, Nelune Cancer Centre, Prince of Wales Hospital, Sydney, Australia; [m]Prince of Wales Clinical School, University of New South Wales, Sydney, Australia; and [n]Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Discipline of Medicine, University of Adelaide, Adelaide, Australia; [o]Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado; and [p]Stanford Cancer Institute, Stanford, California

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Disclosures: Dr Goodman is on the advisory board for RenovoRx, Inc. Dr Chang has received grants from Varian Medical Systems, Inc, and has stock ownership with ViewRay, Inc. All other authors have no conflicts of interest to declare.

* Corresponding author: Andrew Oar, MBBS, MIPH, FRANZCR; E-mail: andrew.oar@icon.team

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Basic Original Report

Incidence and Patterns of Locoregional Failure After Stereotactic Body Radiation Therapy for Pancreatic Adenocarcinoma

Michael J. Baine MD, PhD [a,*], Richard Sleightholm BS [b], Chi Lin MD, PhD [a]

Practical Radiation Oncology® (2021) 11, e63–e69

www.practicalradonc.org

Basic Original Report

Patient-Reported Quality of Life Before and After Chemoradiation for Intact Pancreas Cancer: A Prospective Registry Study

William G. Breen, MD,[a] Krishan R. Jethwa, MD,[b] Nathan Y. Yu, MD,[c] Grant M. Spears, MS,[d] William S. Harmsen, MS,[d] Robert C. Miller, MD,[e] Jonathan B. Ashman, MD, PhD,[c] William G. Rule, MD,[c] Terence T. Sio, MD, MS,[c] Michelle A. Neben-Wittich, MD,[a] Michael G. Haddock, MD,[a] Amit Mahipal, MBBS,[f] Mark J. Truty, MD, MS,[g] Christopher L. Hallemeier, MD,[a] and Kenneth W. Merrell, MD[a,*]

[a]Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; [b]Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut; [c]Department of Radiation Oncology, Mayo Clinic, Phoenix/Scottsdale, Arizona; [d]Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota; [e]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland; [f]Division of Medical Oncology, Mayo Clinic, Rochester, Minnesota; and [g]Department of Surgery, Mayo Clinic, Rochester, Minnesota

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Abstract

Purpose: Our purpose was to determine the effect of chemoradiotherapy (CRT) on patient-reported quality of life (QOL) for patients with intact pancreas cancer.

Methods and Materials: We reviewed a prospective QOL registry for patients with intact, clinically localized pancreatic ductal adenocarcinoma treated with CRT between June 2015 and November 2018. QOL was assessed pre-CRT (immediately before CRT, after neoadjuvant chemotherapy) and at the completion of CRT with the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) and its component parts: FACT-General (FACT-G) and hepatobiliary cancer subscore (HCS). A minimally important difference from pre-CRT was defined as ≥ 6, 5, and 8 points for FACT-G, HCS, and FACT-Hep, respectively.

Results: Of 157 patients who underwent CRT, 100 completed both pre- and post-CRT surveys and were included in the primary analysis. Median age at diagnosis was 65 years (range, 23-90). National Comprehensive Cancer Network resectability status was resectable (3%), borderline resectable (40%), or locally advanced (57%). Folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) (75%) or gemcitabine and nab-paclitaxel (42%) were given for a median of 6 cycles (range, 0-42) before CRT. Radiation therapy techniques included 3-dimensional conformal (22%), intensity modulated photon (55%), and intensity modulated proton (23%) radiation therapy to a median dose of 50 Gy (range, 36-62.5). Concurrent chemotherapy was most commonly capecitabine (82%). Sixty-three patients (63%) had surgery after CRT. The mean decline in FACT-G, HCS subscale, and FACT-Hep from pre- to post-CRT was 3.5 (standard deviation [SD], 13.7), 1.7 (SD 7.8), and 5.2 (SD 19.4), respectively. Each of these changes were statistically significant, but did not meet the minimally important difference threshold. Pancreatic head tumor location was associated with decline in FACT-Hep. Nausea was the toxicity with the greatest increase from pre- to post-CRT by both physician-assessment and patient-reported QOL.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.
Abstract presented at ASTRO annual meeting, September 15 to 19, 2019, Chicago, Illinois.
* Corresponding author: Kenneth W. Merrell, MD; E-mail: Merrell.Kenneth@mayo.edu

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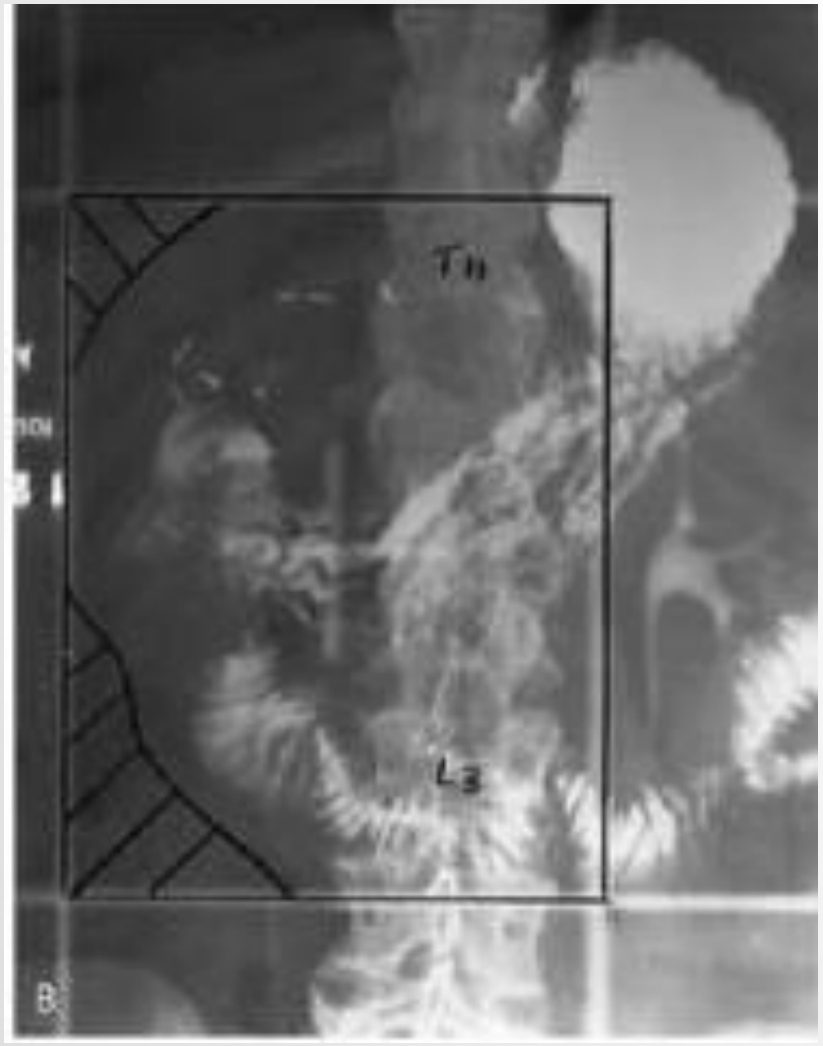
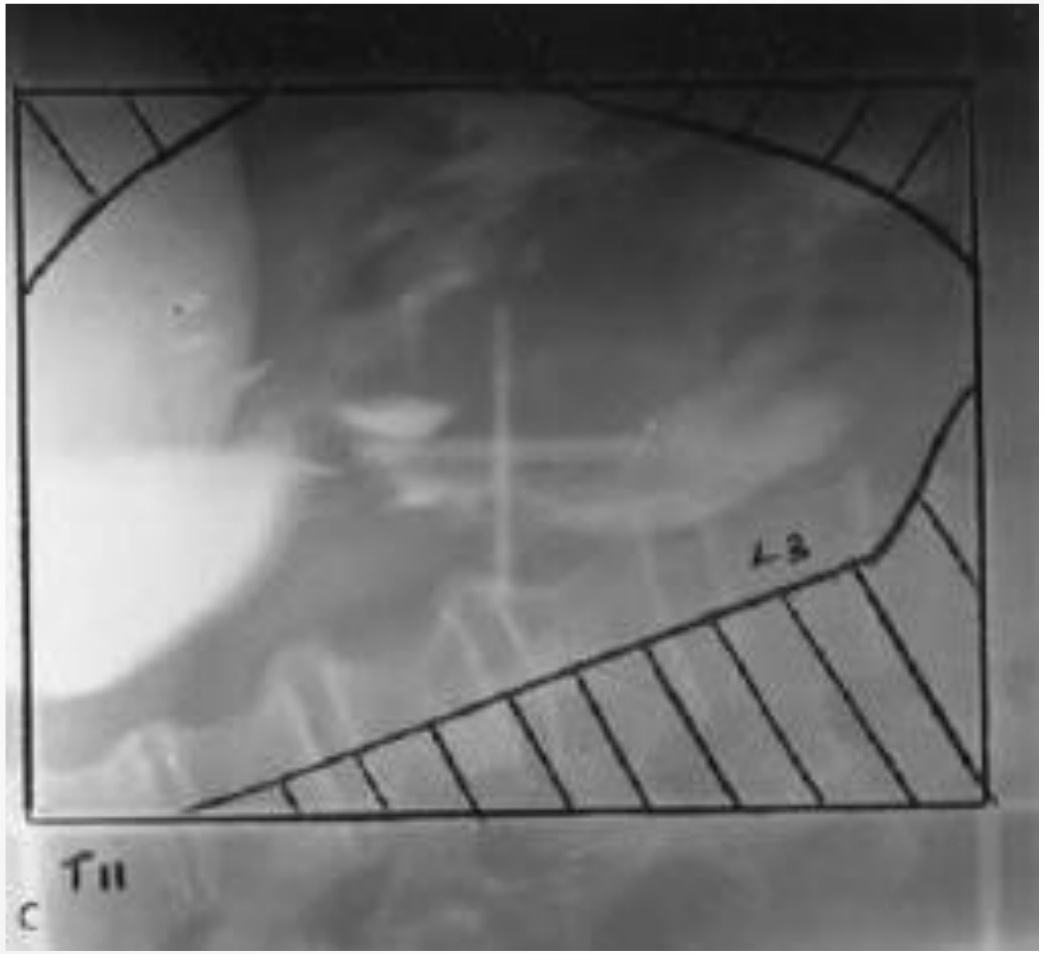
Appropriatezza della Tecnica di Trattamento e dei Volumi Radioterapici





Batch Views Report

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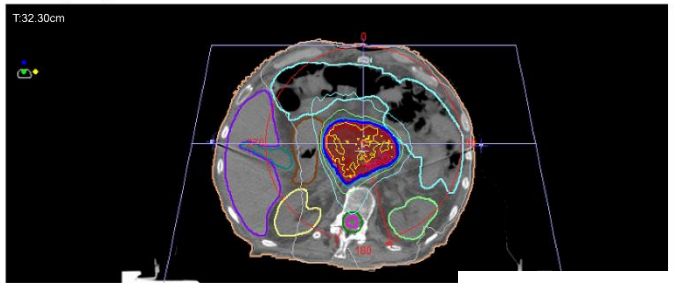
Patient Name:	REGGIANI^MASSIMO	Save Plan Date/Time:	Feb 19, 2021 16:17:47	
Patient ID:	65918	Print Date/Time:	Feb 19, 2021 16:51:42	
Plan Name:	CTplanUnTag:SS_CTplanUnTag:1A	Workstation ID:	SRVMONACO2 10.38.119.14	
Description:	GM			
Comment:	Density overrides used in Monaco calculation Electron densities are overridden on structures that may be overlapped			

SPV Passing Through Plan Isocenter



Color	Dose (Gy)
	59.400
	57.780
	56.700
	54.000
	52.920
	51.300
	48.600
	43.200
	32.400
	10.800

Color	Structure Name
	patient
	Foam Core
	Carbon Fiber
	fegato
	colecisti
	stomaco
	midollo spinale
	rene dx
	rene sn

Approved by: Name: Rita Niespolo Status:

Batch Views Report

Hospital/Clinic:	ASST Monza S.C. Fisica Sanitaria	Doc Numt	
Patient Name:	REGGIANI^MASSIMO	Save Plan	
Patient ID:	65918	Print Date	
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Description:	GM		
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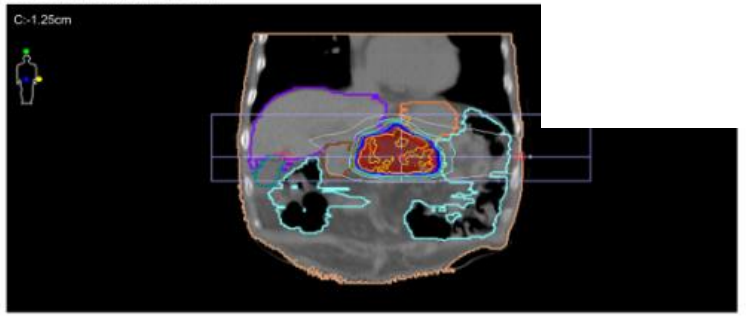

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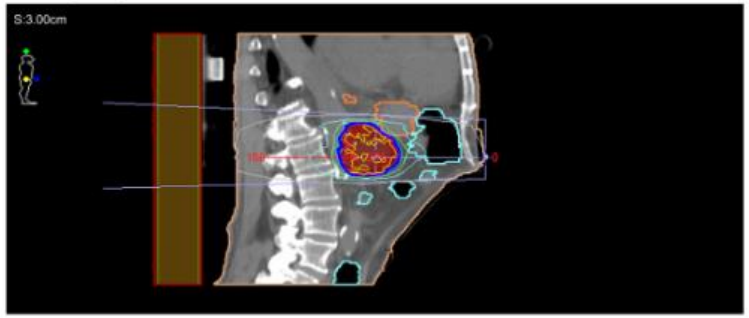
SPV Passing Through Plan Isocenter



Color	Dose (Gy)
	59.400
	57.780
	56.700
	54.000
	52.920
	51.300
	48.600
	43.200
	32.400
	10.800

Color	Structure Name
	patient
	Foam Core
	Carbon Fiber
	fegato
	colecisti
	stomaco
	midollo spinale
	rene dx
	rene sn
	anse intestinali
	duodeno
	ITV
	PRV midollo
	PTV

Key question 6: Indications for palliative RT

Table 7 Recommendation for palliative RT

KQ 6 recommendation	Strength of recommendation	Quality of evidence	Consensus
1. For selected patients with metastatic pancreatic cancer, palliative RT to either the primary or select metastatic sites for symptom management is recommended.	**Strong**	**Moderate**	**100%** *

Abbreviations: KQ = key question; RT = radiation th
* The medical physics representative abstained from

Practical Radiation Oncology® (2020) 10, 274-281

Basic Original Report

The Utility of Stereotactic Ablative Radiation Therapy for Palliation of Metastatic Pancreatic Adenocarcinoma

Amanda J. Koong,[a] Diego A.S. Toesca, MD,[a] J. Richelcyn M. Baclay, MD,[a]
, MS,[a] Albert C. Koong, MD, PhD,[b] and

stitute, Stanford, California and [b]Department of Radiation
r Center, Houston, Texas

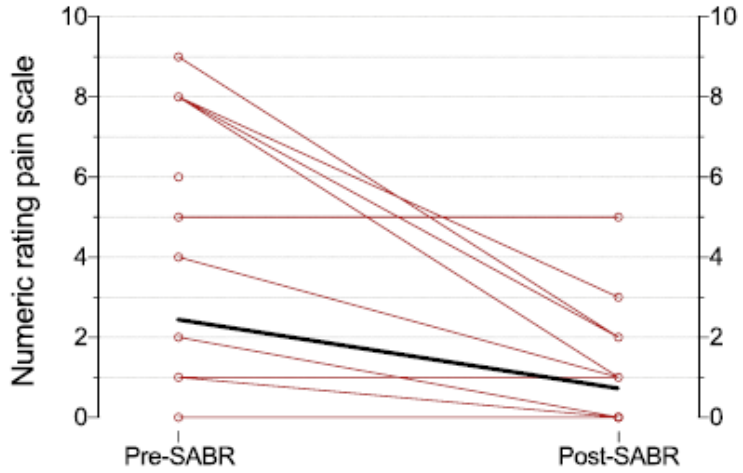


Figure 1 Change in the intensity of pain after stereotactic ablative radiation therapy (SABR) as graded by the numeric rating scale. Pain intensity was graded based on a numeric rating scale, on which patients rated their current pain intensity from 0 ("no pain") to 10 ("worst possible pain").

PRE-CHIRURGIA | POST-CHIRURGIA

RT

DEFINITIVO | PALLIATIVO

ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a,*], Devon Godfrey PhD [a], Karyn A. Goodman MD [b],

ASPETTI TECNICI

RADIOTERAPIA CONVENZIONALE | RADIOTERAPIA STEREOTASSICA

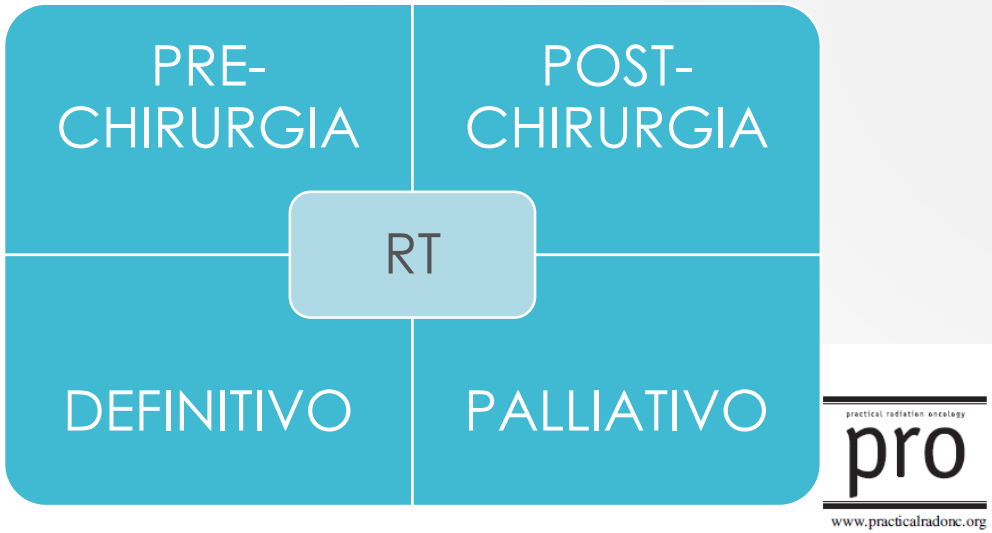
EFFETTI COLLATERALI

Key question 7: Prophylactic medications for toxicity

Table 8 Recommendations for prophylactic medications for toxicity

KQ 7 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with pancreatic cancer undergoing RT, prophylactic use of antiemetic medications to reduce the rate of nausea is recommended.	**Strong**	**Low**	**100%** *
2. For patients with pancreatic cancer undergoing RT, prophylactic use of medications to reduce acid is conditionally recommended.	**Conditional**	**Very Low**	**100%** *

Abbreviations: KQ = key question; RT = radiation therapy.
* One task force member was recused from voting on this KQ based on his disclosures.



ASTRO Guideline

Radiation Therapy for Pancreatic Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Manisha Palta MD [a,*], Devon Godfrey PhD [a], Karyn A. Goodman MD [b],

ASPETTI TECNICI

RADIOTERAPIA CONVENZIONALE

RADIOTERAPIA STEREOTASSICA

EFFETTI COLLATERALI

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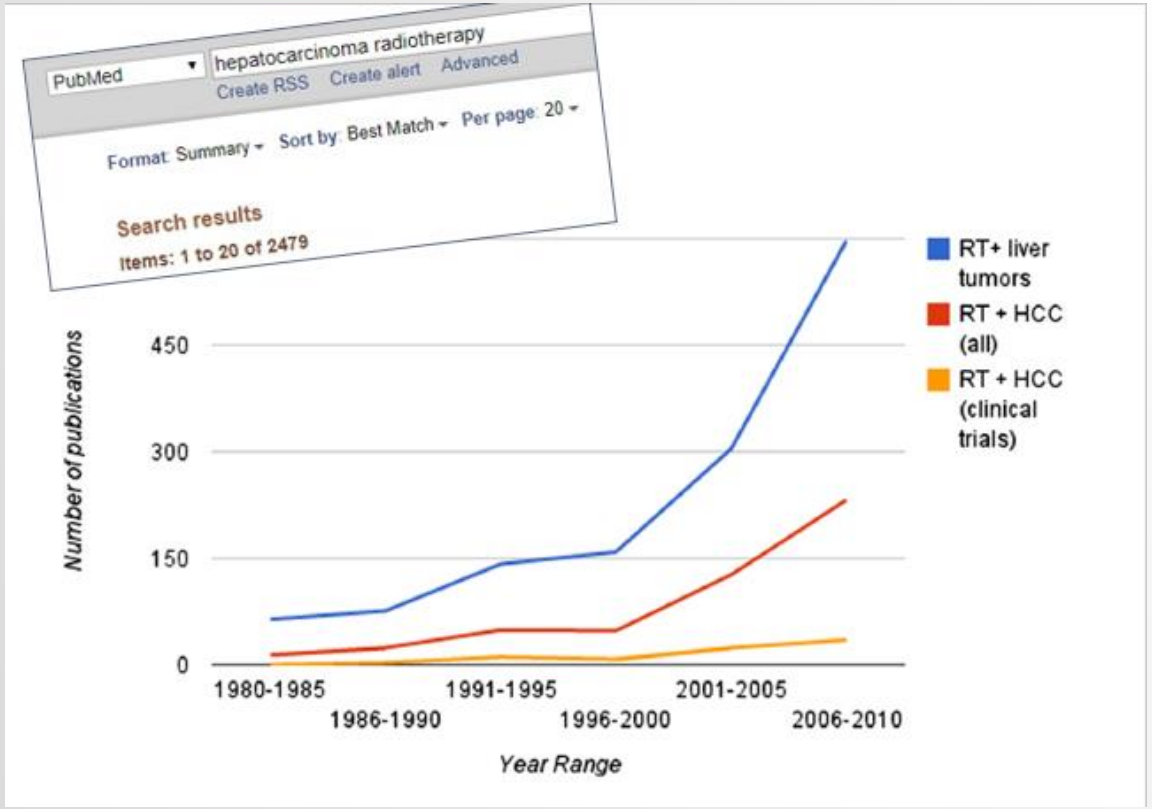

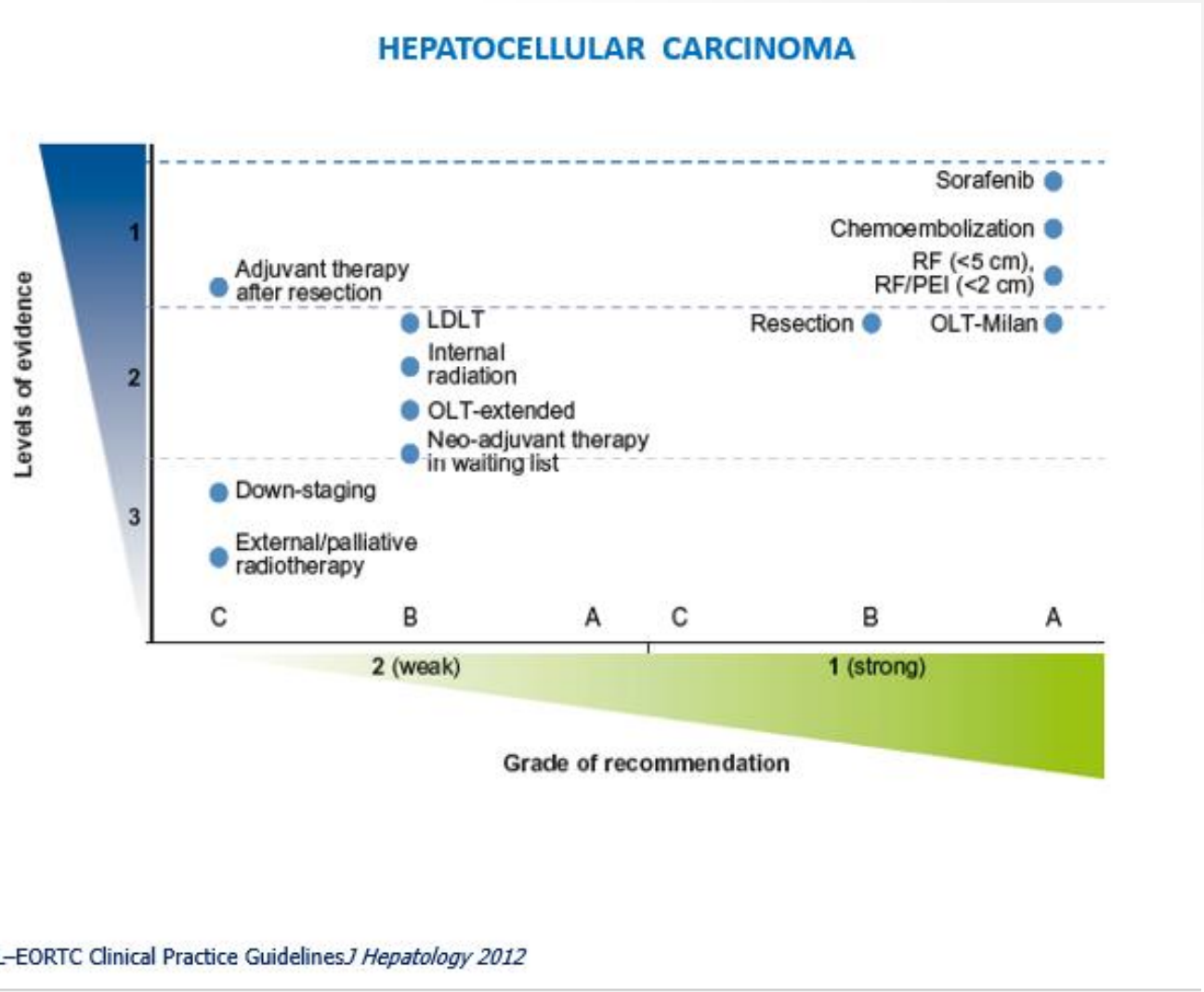

EASL–EORTC Clinical Practice Guidelines *J Hepatology 2012*

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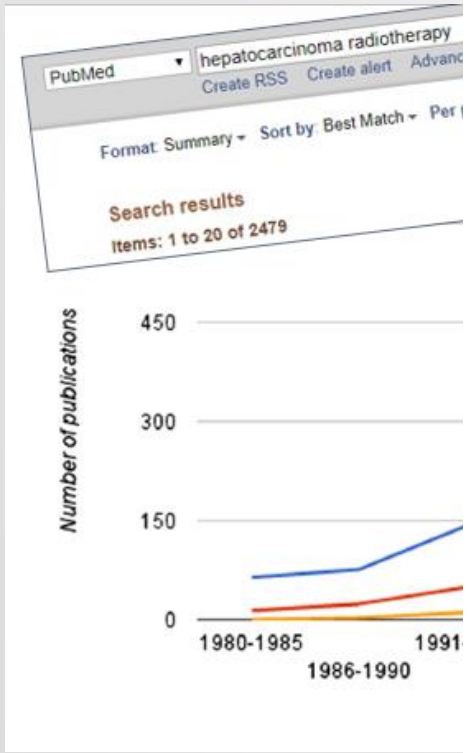


QUANTEC: ORGAN-SPECIFIC PAPER Abdomen: Liver

RADIATION-ASSOCIATED LIVER INJURY

CHARLIE C. PAN, M.D.,* BRIAN D. KAVANAGH, M.D., M.P.H.,† LAURA A. DAWSON, M.D.,‡ X. ALLEN LI, PH.D.,§ SHIVA K. DAS, PH.D.,‖ MOYED MIFTEN, PH.D.,† AND RANDALL K. TEN HAKEN, PH.D.*

Classic Radiation-Induced Liver Disease (RILD)

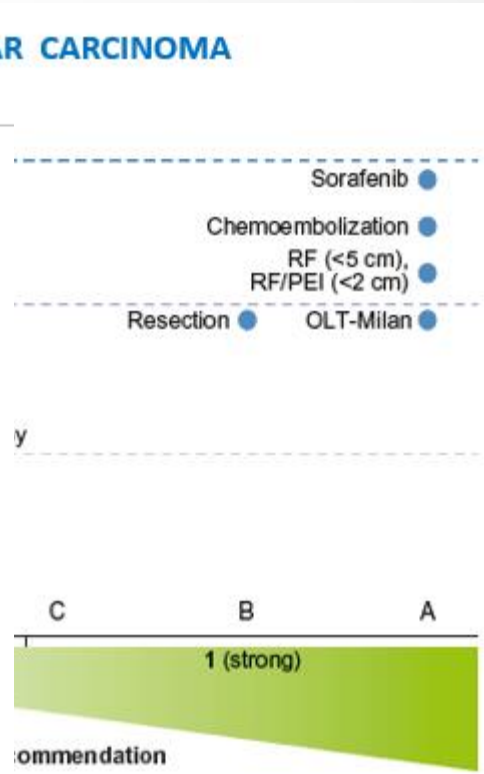
Clinical syndrome of anicteric hepatomegaly, ascites and elevated liver enzymes (more than twice the upper limit of normal or baseline value) typically occuring between 2 weeks to 3 months after therapy

Nonclassic Radiation-Induced Liver Disease (RILD)

typically occuring between 1 weeks to 3 months after therapy, involves elevated liver transaminases more than five times the upper limit of normal or decline in liver function

A confounder of RILD, especially in population with pre-existing liver dysfunction, is the baseline rate of morbidity within this population due to their preexisting liver disease

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S94–S100, 2010



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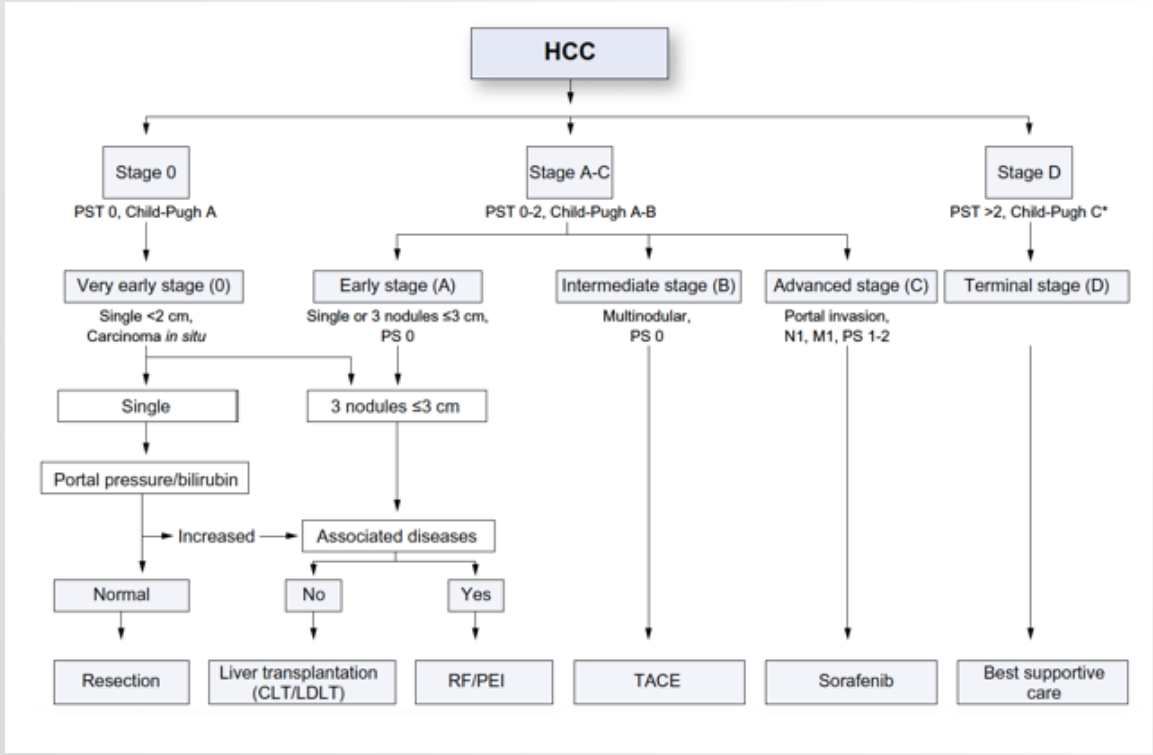
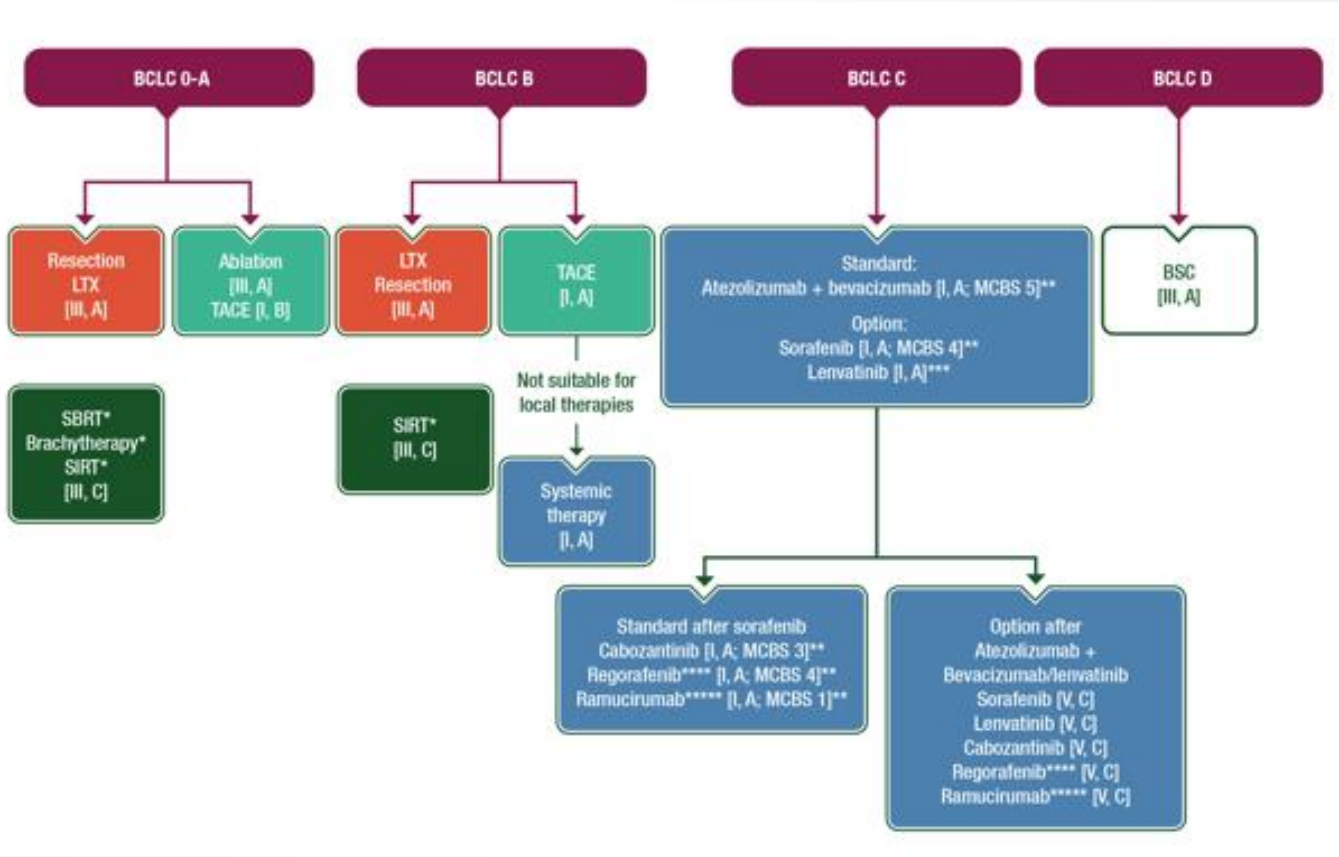
ESMO 2016

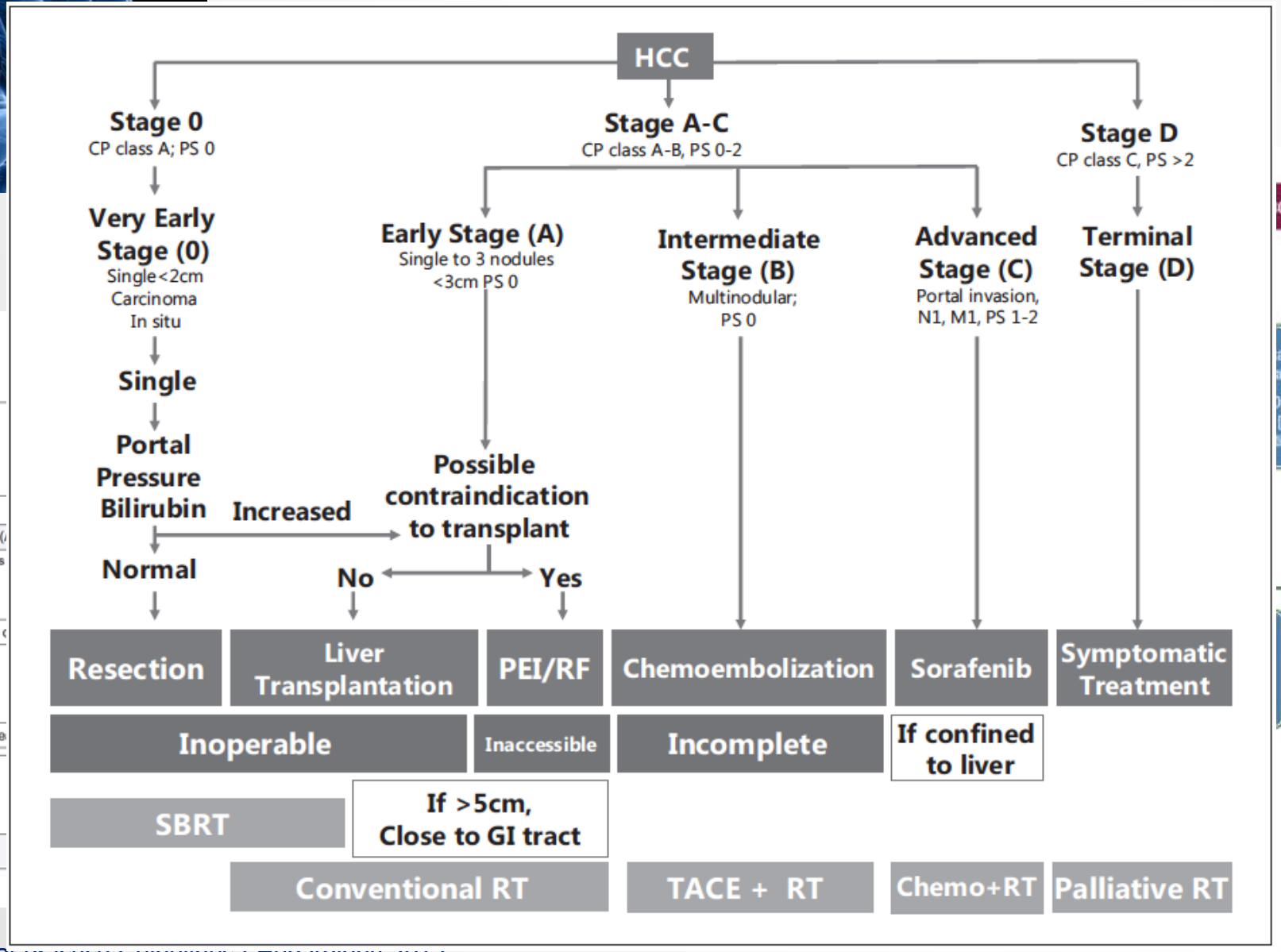


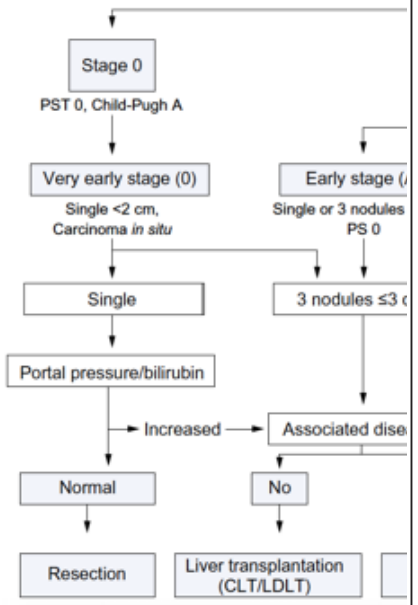


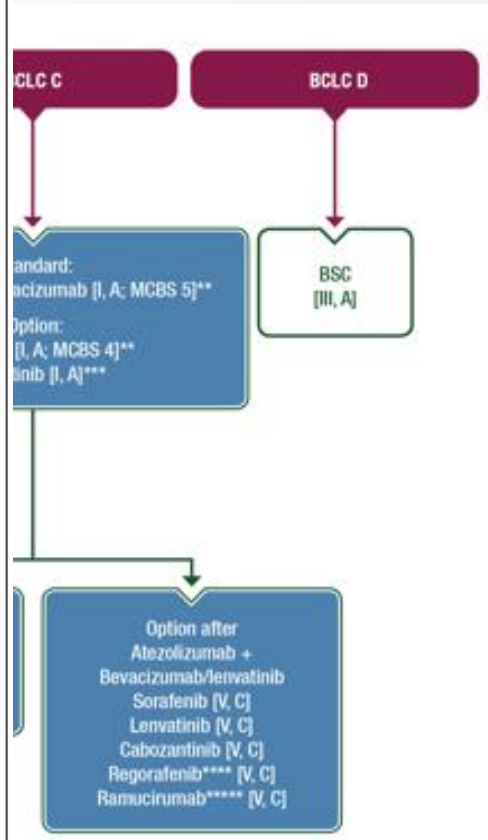
EASL–EORTC Clinical Practice Guidelines *J Hepatology 2012*

Alpha-feto protein?

ESMO 2016





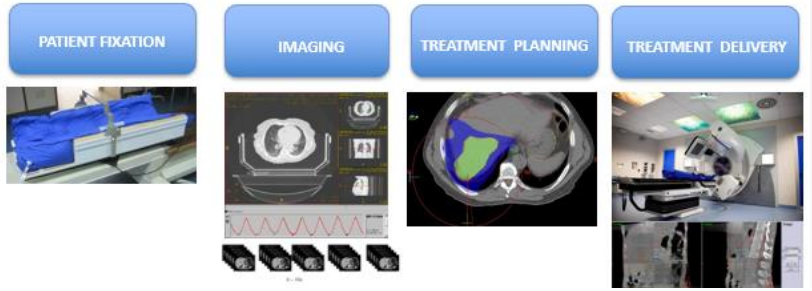


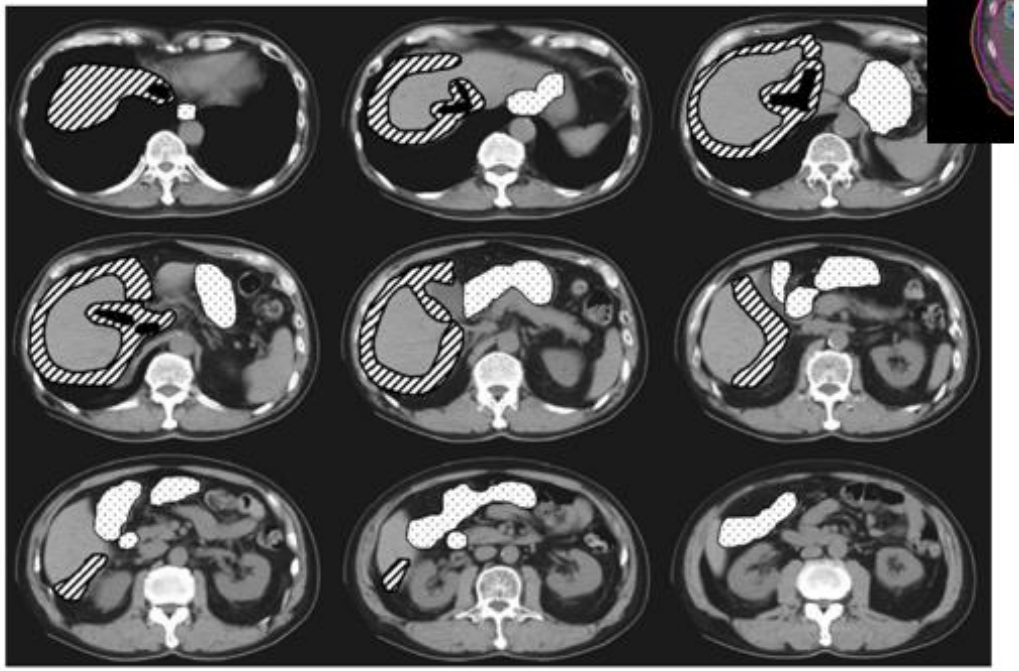
EASL–EORTC Clinical Practice Guidelines *J Hepatology 2012*

RT is applicable for HCC patients at each BCLC stage

WHAT IS THE ROLE OF RT IN HCC?

	Surgery	Percutaneous ablative therapy	TACE	SBRT
Tumor size	< 5 cm (or more)	< 3 cm	> 3-5 cm	4 (or 5) cm
Number of tumors	< 3	Depends on location	1-multiple (> 4)	< 1-3
Location or characteristics	Depends on liver function	Away from large vessels or biliary system	Hypervascu-lar lesions	Away from bowels
Local control (2 yr)	> 90%	> 90%	< 65%	> 90%
Level of evi-dence	High	Intermediate-high	Intermediate-high	Low
Invasiveness	High	Less	Less	None
Damage to the liver	High	Low	Low-moder-ate	Low-moderate





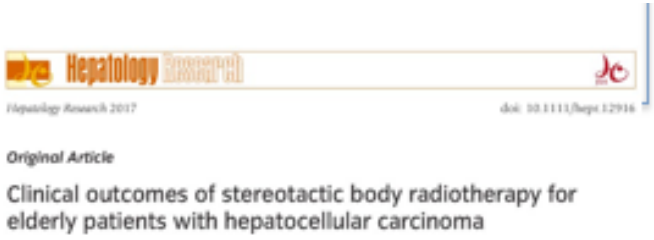
Typical liver locations for which SBRT can be safely delivered

Typical liver locations for which SBRT is not easily suitable

SABR FOR HCC

Eligibility Criteria
Appropriate Patient selection

1. Histological or radiological confirmation of HCC
2. Single lesion with/without satellite nodules
3. Multiple lesions: number ≤3, diameter ≤6 cm
4. Child-Pugh A-B7
5. No extrahepatic disease (N1-M1)
6. Tumor vascular thrombosis (TVT)
7. PS ECOG 0-1



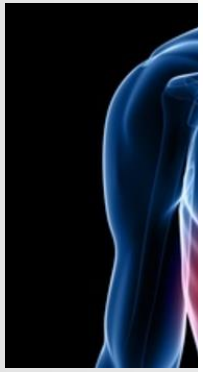
Original Article

Clinical outcomes of stereotactic body radiotherapy for elderly patients with hepatocellular carcinoma

SABR FOR HCC

Clinical Indications

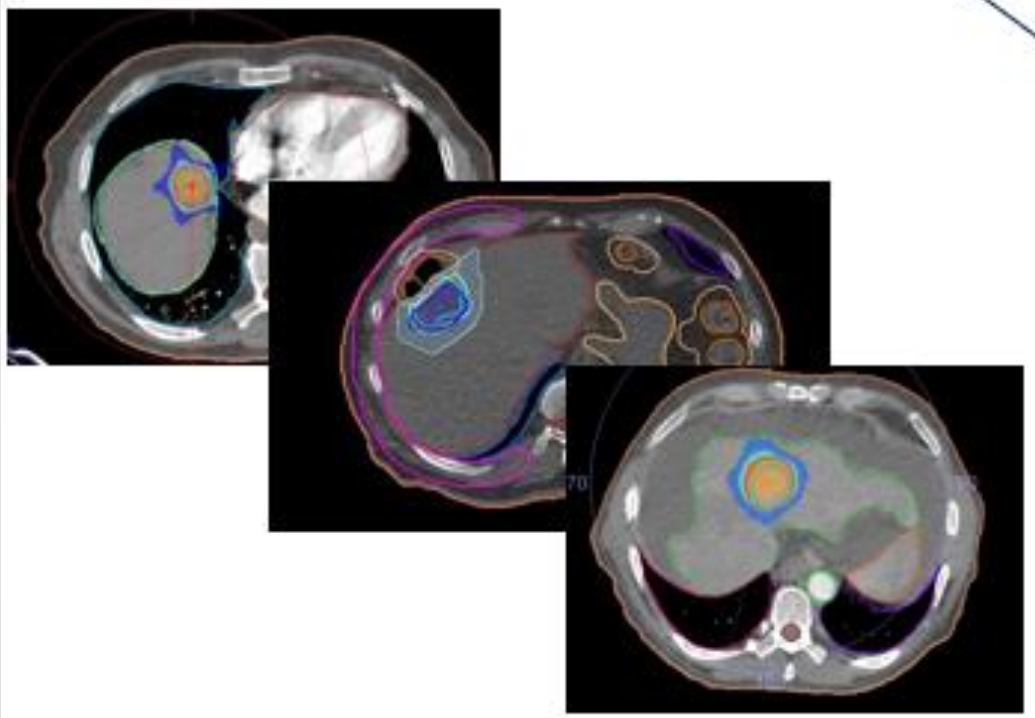
1. Surgery and loco-regional treatment contraindicated or refused
2. Recurrent HCC after loco-regional treatment
3. HCC BCLC B in association with loco-regional treatment (e.g TACE)
4. As a bridge to liver trasplantation
5. Neoadjuvant to liver trasplantation or local treatment (downstaging)



SBRT Dose: Risk-adapted approach

HCC Child A	48 Gy/3 fractions iso-80%
HCC Child B 7	36 Gy/3 fractions iso-80%
HCC Child B 8-9	**WARNING**
HCC adjacent to the central biliary system	40 Gy/5 fractions iso-80%

Child B ≥8: the strongest predictor of RILD



Acceptable Toxicity After Stereotactic Body Radiation Therapy for Liver Tumors Adjacent to the Central Biliary System

Takahisa Eriguchi, MD,* Atsuya Takeda, MD, PhD,* Naoko Sanuki, MD,* Yohei Oku, PhD,* Yousuke Aoki, RTT, BMSc,* Naoyuki Shigematsu, MD, PhD,† and Etsuo Kunieda, MD, PhD‡

International Journal of Radiation Oncology biology • physics Official Journal of the American Society for Radiation Oncology ASTRO

April 1, 2015 Volume 91, Issue 5, Pages 986–994

96 paz.

53% primay liver tumors
47% metastatic liver tumors

Predictors of Toxicity Associated With Stereotactic Body Radiation Therapy to the Central Hepatobiliary Tract

esented at the 56th Annual Meeting of the American Society for Radiation Oncology, San Francisco, CA, September 14-17, 2014.

an C. Osmundson, MD, PhD , Yufan Wu, BHSc, Gary Luxton, PhD, Jose G. Bazan, MD, MS, Albert C. Koong, MD, PhD, Daniel T. Chang, MD

Il tratto centrale HB (cHBT) è stato definito da un'espansione di 15 mm che parte dalla confluenza splenica alla prima biforcazione delle vene porta sinistra e destra.

Per confrontare differenti frazionamenti SBRT, le dosi sono state convertite in dosi biologicamente efficaci (BED) utilizzando il modello quadratico lineare standard $\alpha / \beta = 10$ (BED10).

VBED10 72 e VBED10 66 sono corrispondenti a V40 e V37.7 per 5 frazioni e V33.8 e V32 per 3 frazioni.

Med Oncol (2016)33:104
DOI 10.1007/s12032-016-0823-z

ORIGINAL PAPER

Stereotactic ablative radiotherapy in the treatment of hepatocellular carcinoma >3 cm

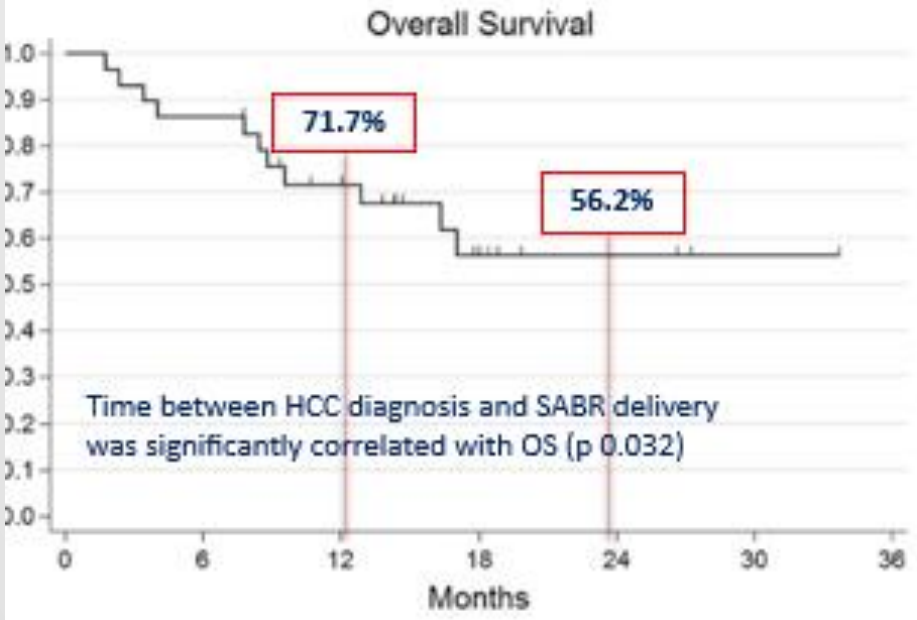
Alessia Guarneri[1] · Pierfrancesco Franco[2] · Elisabetta Trino[2] · Daniela Campion[3] · Riccardo Faletti[4] · Stefano Mirabella[5] · Silvia Gaia[6] · Riccardo Ragona[2] · Margherita Diotallevi[3] · Giorgio Saracco[3] · Mauro Salizzoni[5] · Umberto Ricardi[2] · Patrizia Carucci[6]

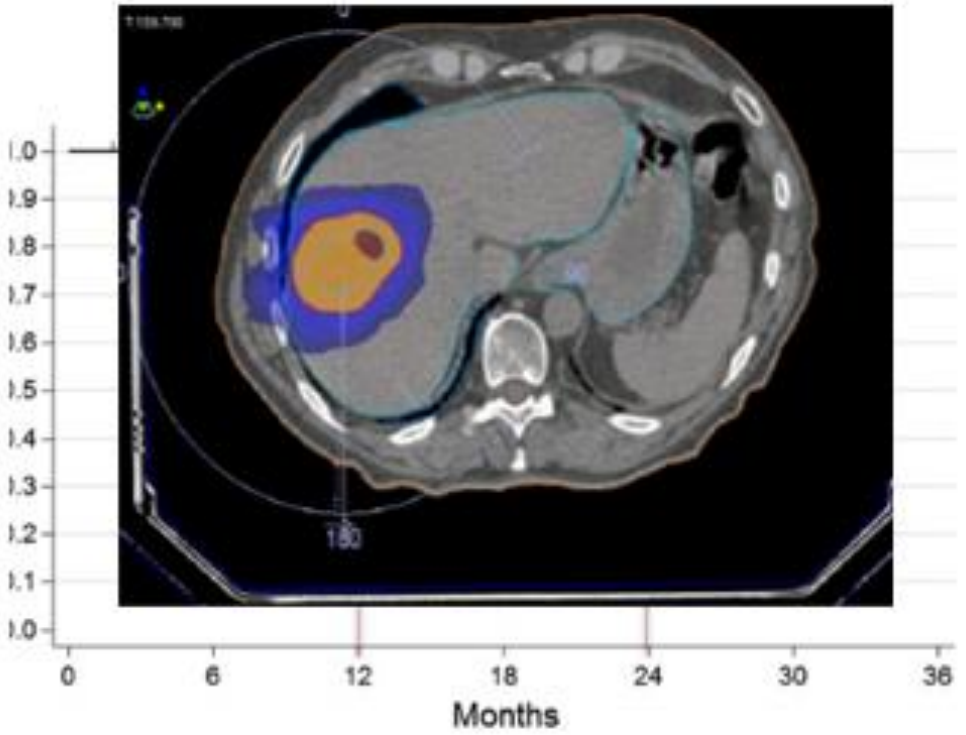
29 patients with at least one lesion >3 cm

Lesion size: range 31-120 mm, median 47 mm

Median follow-up time of 18 months

No local failure was observed





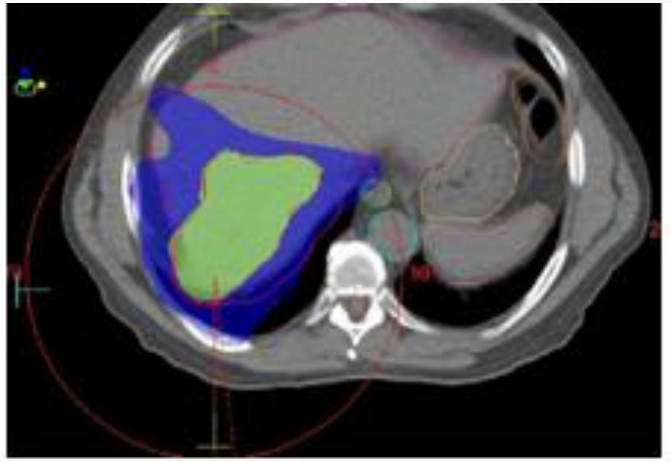
SABR provided LC and survival rates comparable to other local therapies for patients with HCC lesion sized >3 cm, with acceptable toxicity profile (RILD 6%)

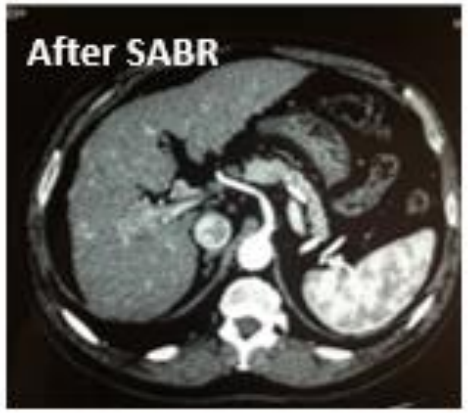
Stereotactic body radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma with portal vein tumor thrombosis

JINGBO KANG , QING NIE, RUI DU, LIPING ZHANG, JUN ZHANG, QILIANG LI, JIANGUO LI and WENJIE QI

Effectiveness of Stereotactic Body Radiotherapy for Hepatocellular Carcinoma with Portal Vein and/or Inferior Vena Cava Tumor Thrombosis

Mian Xi*, Li Zhang*, Lei Zhao, Qiao-Qiao Li, Su-Ping Guo, Zi-Zhen Feng, Xiao-Wu Deng, Xiao-Yan Huang, Meng-Zhong Liu





PORTAL VEIN THROMBOSIS

- PTV is a poor prognostic factor (precludes surgery and arterial-directed therapies)
- HCC with PVT often liver confined, potentially suitable for treatment with radiation therapy (RT) – Recanalization post RT occurs in ~ 50% (30-80%) – Median survival post RT ~ 9 mo (~5–17 mo)
- However it is a slow process (median time to maximal response 6 months)

Klein, IHROBP 2013; Bujold JCO 2013

SABR - Follow up

Revue générale

Suivi après radiothérapie stéréotaxique des tumeurs hépatiques : revue de la littérature et recommandations

Follow-up after stereotactic body radiation therapy for liver tumours: A review of the literature and recommendations

G. Janoray[a,*], F. Morenc[b,c]

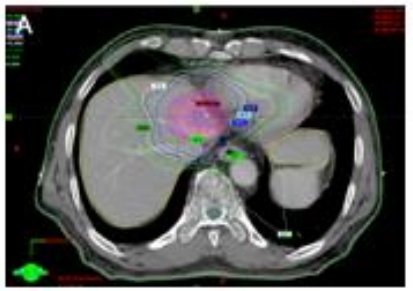
Target lesions		
Response category	RECIST	mRECIST
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as re the diameters of target les	At least a 30% decrease in the sum of the diameters
SD	Any cases that do not qua	
PD	An increase of at least 20 of target lesions, taking as the diameters of target les started	
Non-target lesions		
Response category	RECIST	
CR	Disappearance of	
IR/SD	Persistence	
PD	Appearance of unequivocal pro	
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmatio required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at cm.	
Portal vein thrombosis	Malignant portal vein thro target lesion group.	
New lesion	A new lesion can be class typical for HCC. A lesion interval growth.	

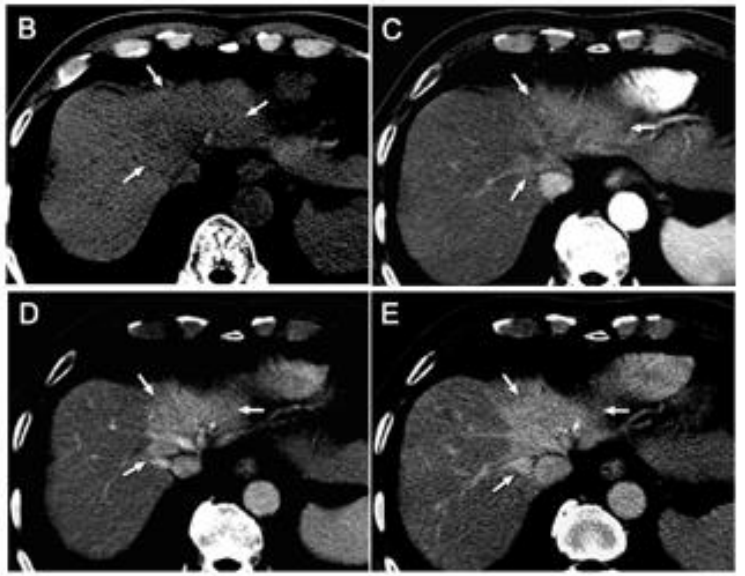
RECIST, Response Evaluation Criteria In Solid Tumors; mREC incomplete response; SD, stable disease; PD, progressive dis [a]Adapted from Llovet et al. [149] and Lencioni and Llovet [1

PLOS ONE | www.plosone.org February 2014

Stereotactic Body Radiotherapy-Induced Arterial Hypervascularity of Non-Tumorous Hepatic Parenchyma in Patients with Hepatocellular Carcinoma: Potential Pitfalls in Tumor Response Evaluation on Multiphase Computed Tomography

Mee Jin Park[1*], So Yeon Kim[1*], Sang Min Yoon[2], Jong Hoon Kim[3], Seong Ho Park[1], Seung Soo Lee[1], Yedaun Lee[1], Moon-Gyu Lee[1]





Recommandations concernant le suivi après radiothérapie stéréotaxique hépatique.

	Avant le traitement	1 fois par semaine pendant le traitement	À la fin du traitement	3 à 4 semaine
Examen clinique	X	X		X
Examen biologique	X	X		X
Examen radiologique	Tomodensitométrie ou IRM			
Évaluation de la toxicité	X	X		X
Assurance qualité	X		X	

AJR:202, January 2014

Added Value of Diffusion-Weighted MRI for Evaluating Viable Tumor of Hepatocellular Carcinomas Treated With Radiotherapy in Patients With Chronic Liver Disease

Hyun Jeong Park[1,2]
Seong Hyun Kim[1]
Kyung Mi Jang[1]
Sanghyeok Lim[1]
Tae Wook Kang[1]
Hee Chul Park[1]
Dongil Choi[1]

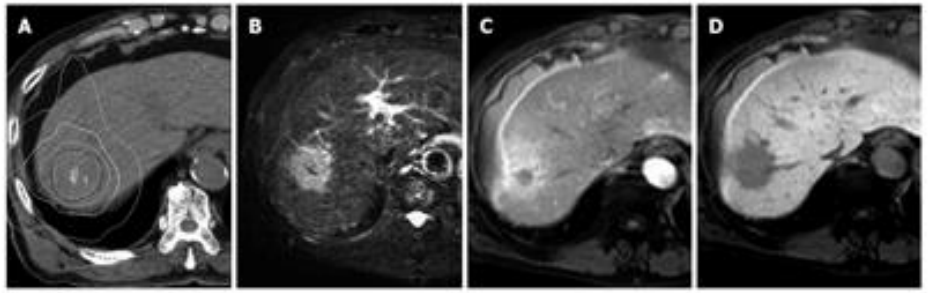
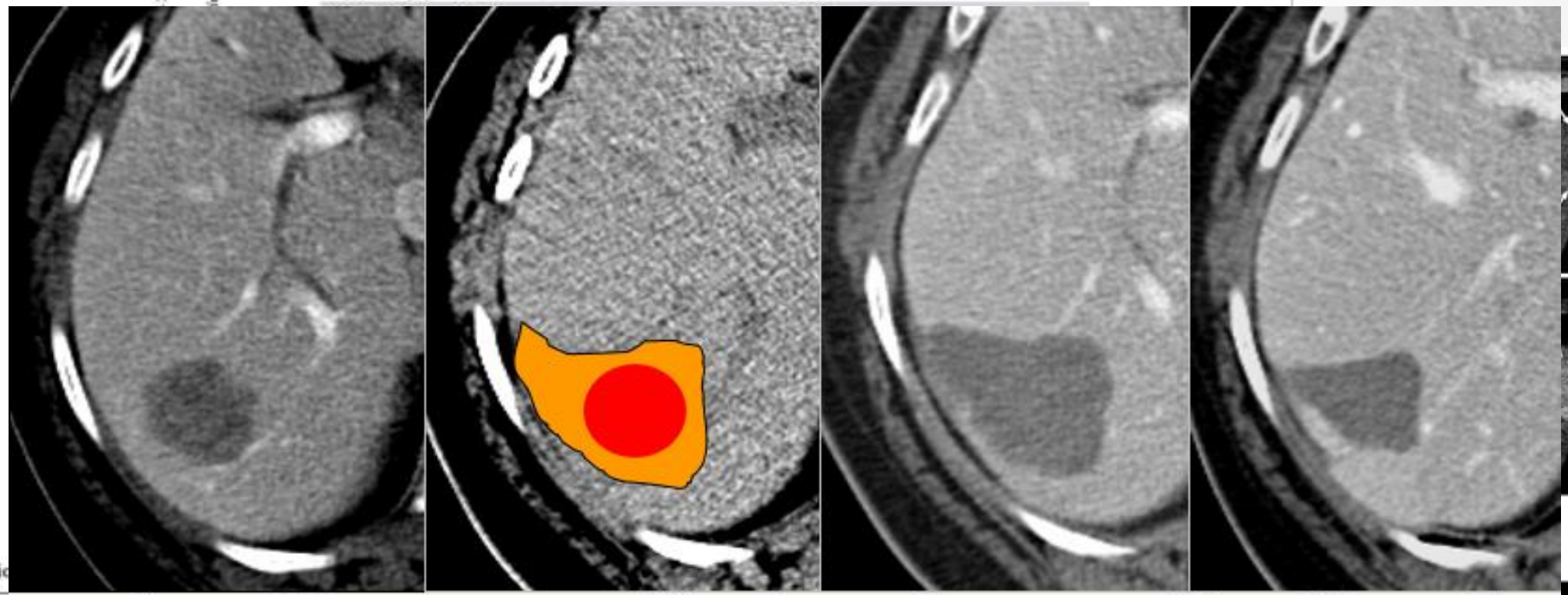


Figure 7 Typical focal liver reaction 4 mo after stereotactic body radiation therapy seen on gadoxetate acid-enhanced magnetic resonance imaging. An axial view of radiation dose distribution (A). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively. A T2-weighted image shows a high-intensity area corresponding to a high-dose area (B), which is seen as an enhanced area in early phase after injection of gadoxetate acid (C). The hepatobiliary phase shows a well-demarcated low-intensity area (D).

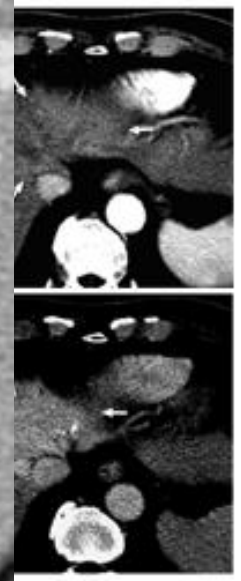
SABR - Follow up



Pre - RF

After 1 month

After 12 months



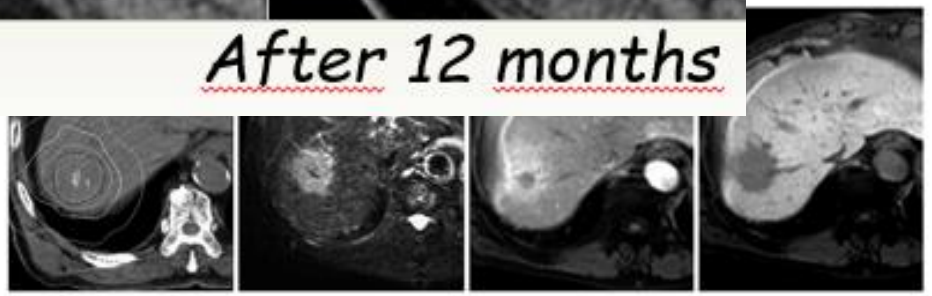


Figure 7 Typical focal liver reaction 4 mo after stereotactic body radiation therapy seen on gadoxetate acid-enhanced magnetic resonance imaging. An axial view of radiation dose distribution (A). The isodose lines (white lines) from inner to outer represent 40, 30, 20, and 10 Gy, respectively. A T2-weighted image shows a high-intensity area corresponding to a high-dose area (B), which is seen as an enhanced area in early phase after injection of gadoxetate acid (C). The hepatobiliary phase shows a well-demarcated low-intensity area (D).

Target lesions

Response category RECIST mRECIST

Recommandatic

traitement

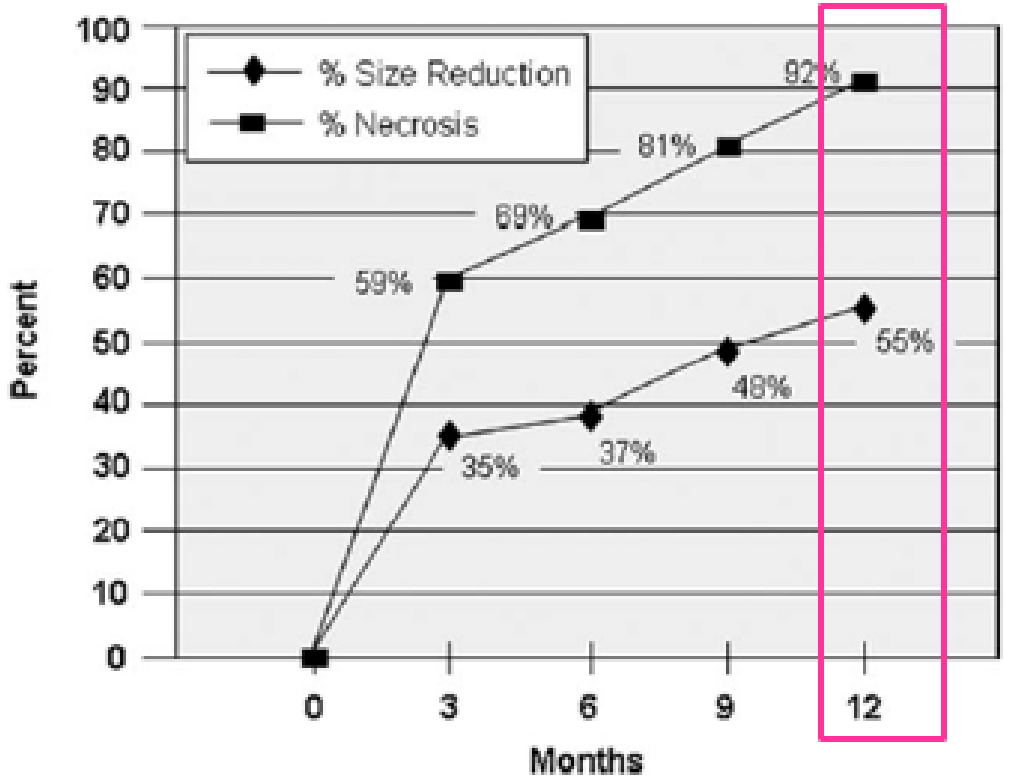
Examen clinique	X	X		X
Examen biologique	X	X		X
Examen radiologique	Tomodensito-métrie ou IRM			
Évaluation de la toxicité	X	X		X
Assurance qualité	X		X	

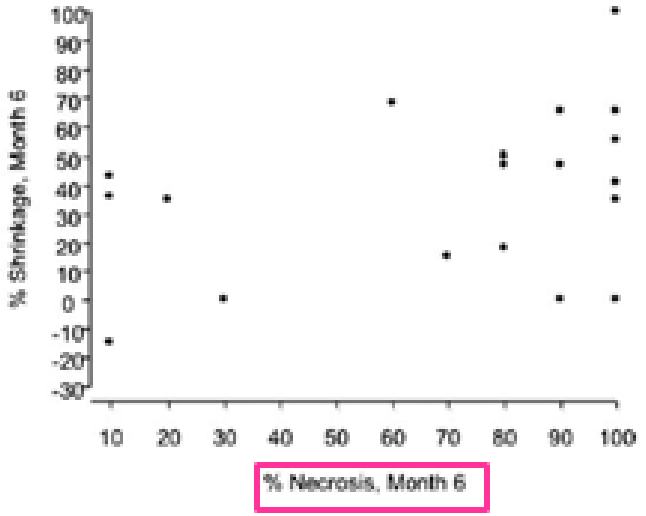
MRI for Evaluating Viable Tumor of Hepatocellular Carcinomas Treated With Radiotherapy in Patients With Chronic Liver Disease

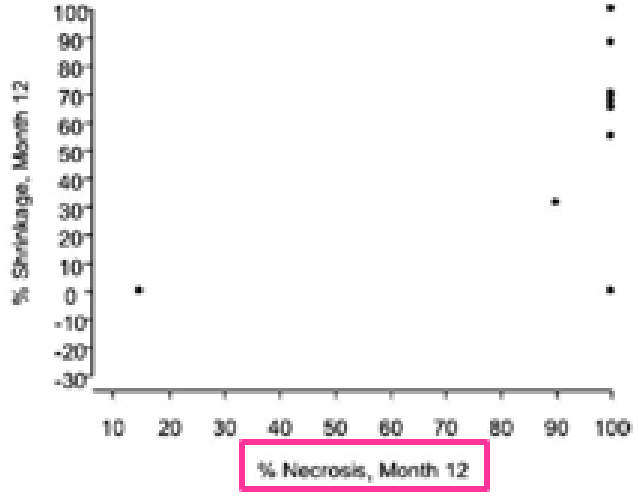
Hyun Jeong Park[1,]
Seong Hyun Kim[1]
Kyung Mi Jang[1]
Sanghyeok Lim[1]
Tae Wook Kang[1]
Hee Chul Park[1]
Dongil Choi[1]

Evaluation of Response After Stereotactic Body Radiotherapy for Hepatocellular Carcinoma*

Tracy R. Price, MD[1]; Susan M. Perkins, PhD[2]; Kumar Sandrasegaran, MBm, ChB[3]; Mark A. Henderson, MD[1]; Mary A. Maluccio, MD[4]; Jennifer E. Zook, MD[1]; A. Joseph Tector, MD, PhD[4]; Rodrigo M. Vianna, MD[4]; Peter A.S. Johnstone, MD[1]; and Higinia R. Cardenes, MD, PhD[1]

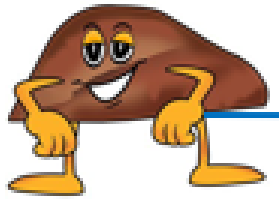






Percentage necrosis was greater than percentage size reduction at each point in time and the magnitude of difference increased at each point.

Cancer 2012;118:3191-8.



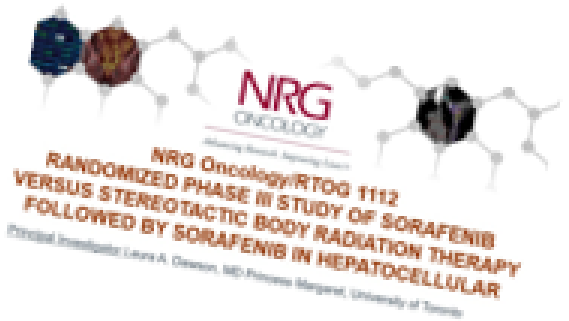
Future developments

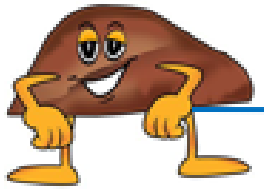
- Further studies are needed to refine patient selection, dose prescription, and ideal utilization of SBRT.

- Little is known about the tolerance of the liver to re-irradiation

- Given the risk of HCC recurrence outside the irradiated volume, especially for advanced-stage HCC, there is rationale to combine RT with regional or systemic therapies, but currently with limited evidence.

- Sorafenib has efficacy as a single agent. Preliminary work combining it with RT for HCC has shown potential for long-term HCC control, but with increased toxicity.





Fu

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- Little is known about the tol
- Given the risk of HCC recu
  advanced-stage HCC, there
  therapies, but currently with
- Sorafenib has efficacy as a s
  combining it with RT for HC
  long-term HCC control, but

Take home messages

There is a growing clinical experience in HCC RT with promising clinical outcomes

SAFE

high doses well tolerated in patients with normal underlying liver function

EFFECTIVE

recent prospective studies of more focal RT for liver tumors suggest that higher doses associated with good local control

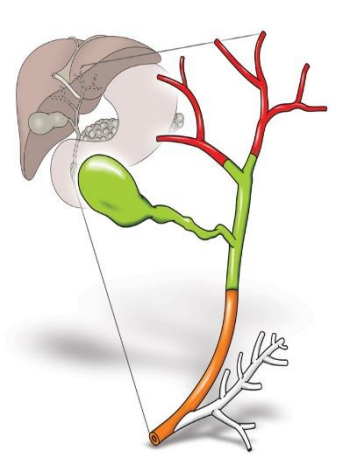
CAUTION

SABR may not be appropriate in patients with underlying liver dysfunction

CC colecisti.

Chemioterapia (Gemcitabina-CDDP) o chemio RT:

- Adiuvante: pT2-T4 N0-N+; R1/G3, PNI, LVI, età ≤50
- Malattia localmente avanzata inoperabile



CCI e CCE.

Chemioterapia (Gemcitabina-CDDP) o chemioRT:

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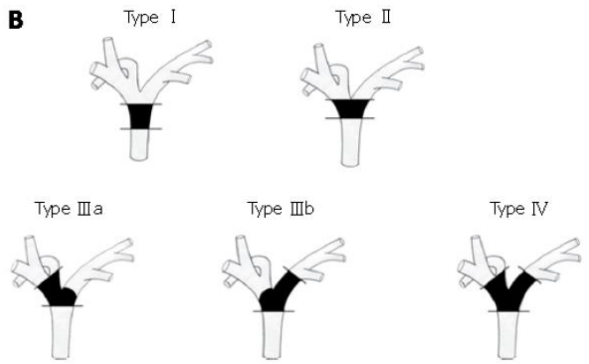
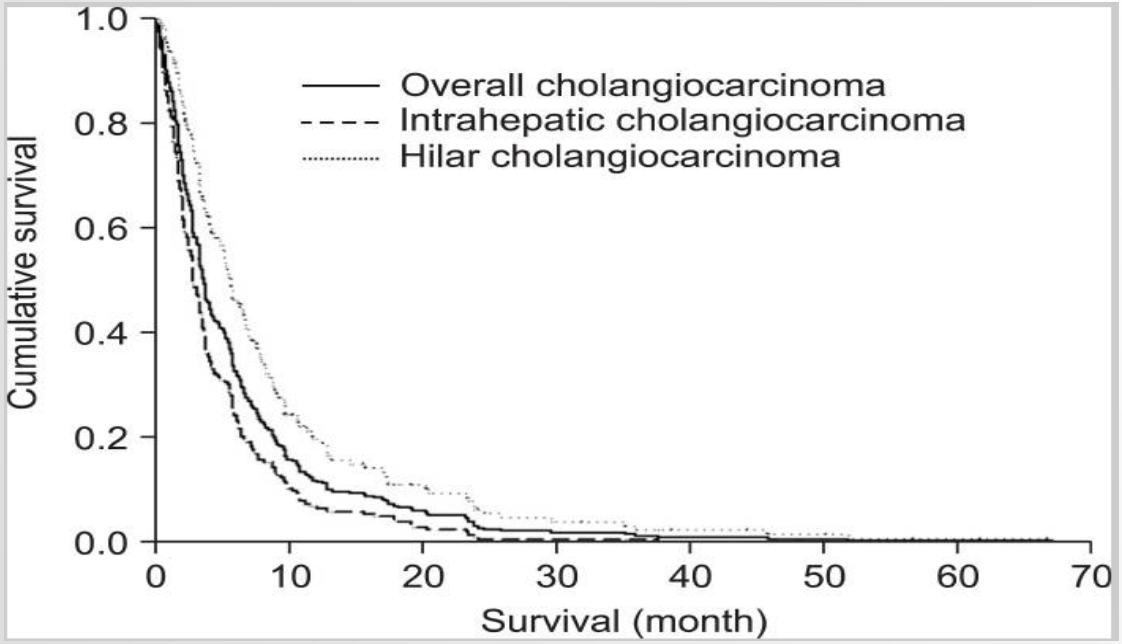


(Urego M et al, IJROBP1999, Leong E et al J GI Cancer 2012, Morganti AG et al. IJROBP2000, Crane CH et al IJROBP 2002, Ben-David MA et al IJROBP 2006).

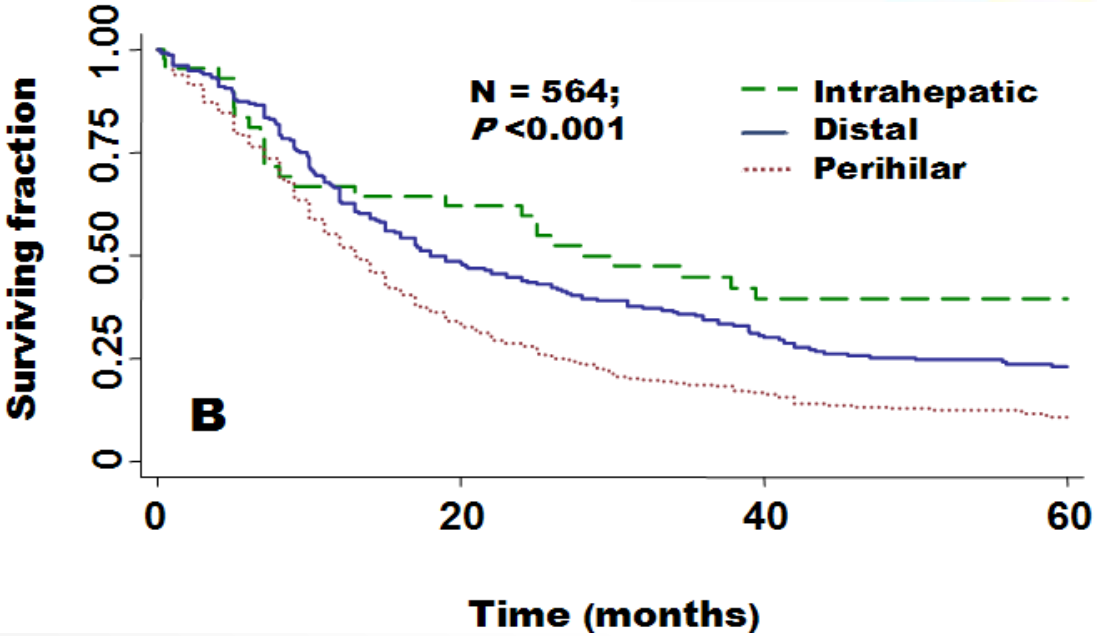
La chirurgia unico trattamento con finalità curativa

Non Trattati

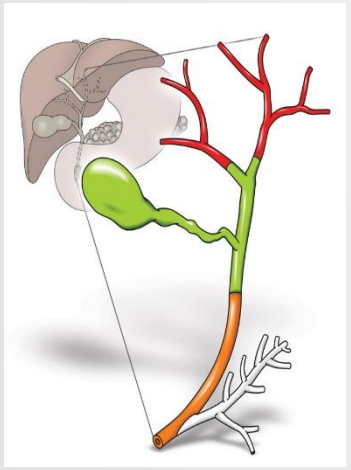


Prk J, GUT Liver 2009

Trattati



DeOliveira LM, Ann Surg, 2007

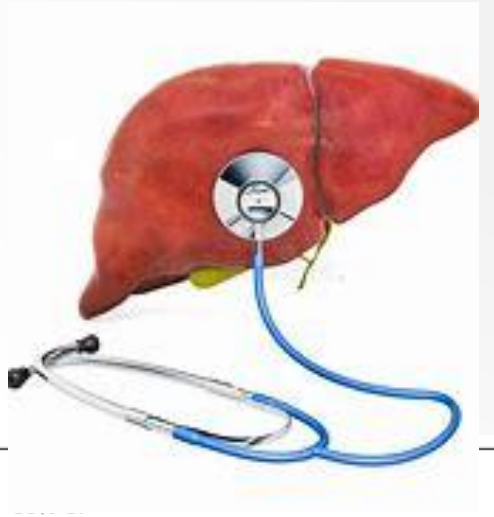


VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adjuvant Therapy in the Treatment of Biliary Tract Cancer: A Systematic Review and Meta-Analysis

Anne M. Horgan, Eitan Amir, Thomas Walter, and Jennifer J. Knox



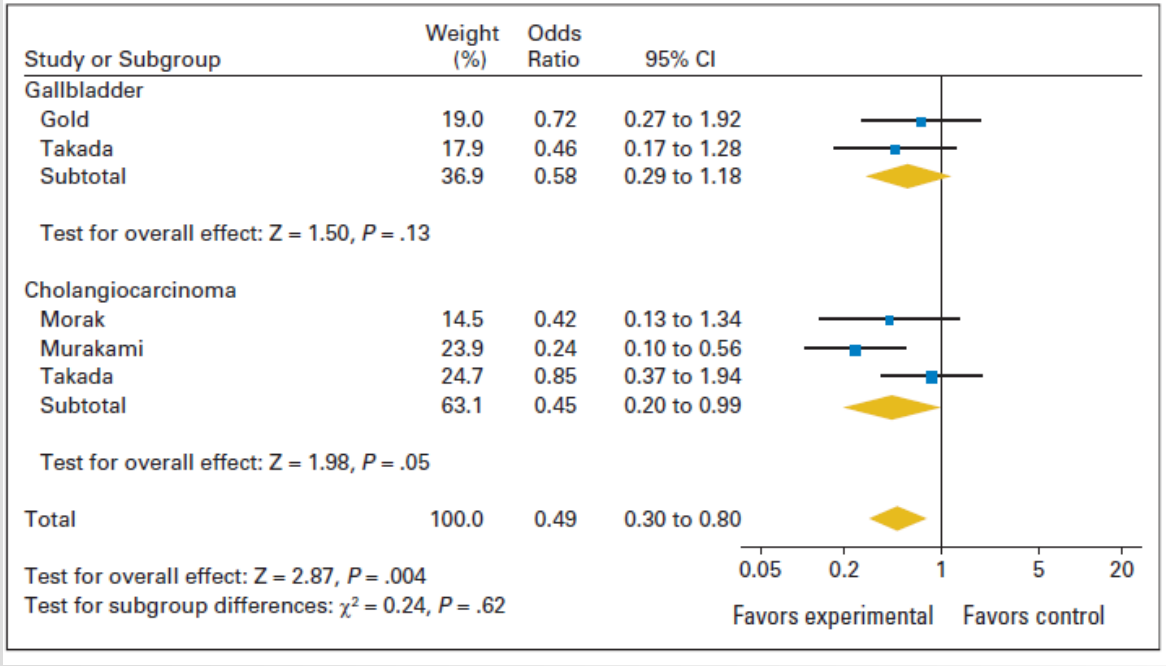


Fig 3. Efficacy outcomes for node-positive disease.

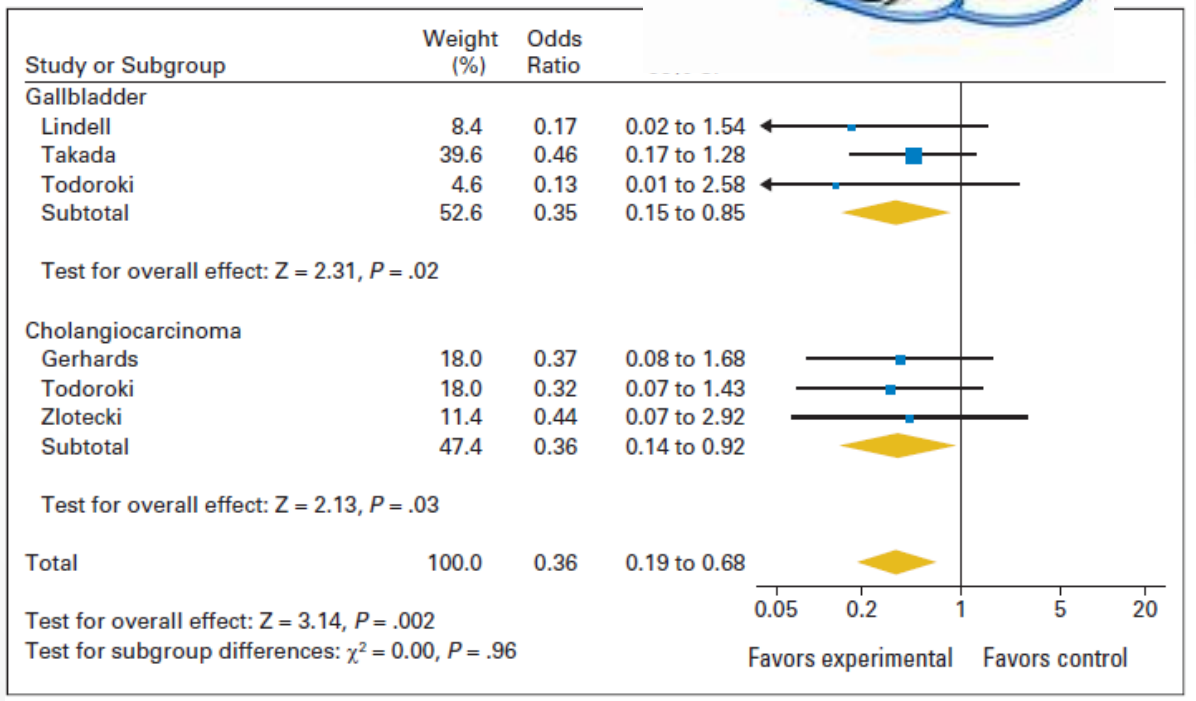
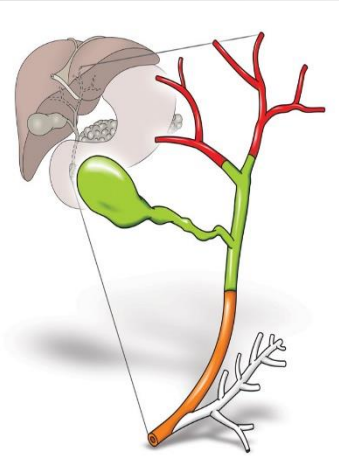


Fig 4. Efficacy outcomes for margin-positive disease.



VOLUME 33 · NUMBER 24 · AUGUST 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

SWOG S0809: A Phase II Intergroup Trial of Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma

Criteri di inclusione e trattamento.

- stadio: pT2-T4 o N+ o R1
- PS 0-1

- CT induzione: 4 cicli GEMCITABINA-CAPECITABINA
- Fase concomitante: RT-CAPECITABINA
- Dose RT

3D: 45Gy/25 fr + boost 9-14.4Gy/5-8 fr – totale 54-59.4Gy (R0 o R1)
IMRT-SIB: 45-52.5Gy/25 fr (R0) o 45-55Gy/25 fr (R1)
Volumi RT: LN VP, TC e pancreatico-duodenali – letto tumorale

Basi razionali e dati statistici

-Ripresa di malattia locoregionale/distanza nel 39-69% casi
- 2y OS: 55% in R0 e 38% in R1

- DEFINIZIONE efficacia: 2yOS>45%; se R0≥60%; se R1≥45%
- Campione: 80 pz; stratificazione per sede e tipo chirurgia

Colangiocarcinoma: ruolo SBRT

SBRT

- **Patients inelegible for resection**
- **After surgery with positive margins (R+)**

Best Pract Res Clin Gastroenterol. 2016 Aug;30(4):603-16. doi: 10.1016/j.bpg.2016.06.003. Epub 2016 Jun 25.

Stereotactic body radiation therapy for primary and metastatic liver tumors: From technological evolution to improved patient care.

Méndez Romero A[1], de Man RA[2].

When biologically effective doses were > 80.5Gy, three-year local control was 78% vs. 45% with lower doses.

MOLECULAR AND CLINICAL ONCOLOGY 15: 152, 2021

Stereotactic radiotherapy in intrahepatic cholangiocarcinoma: A systematic review

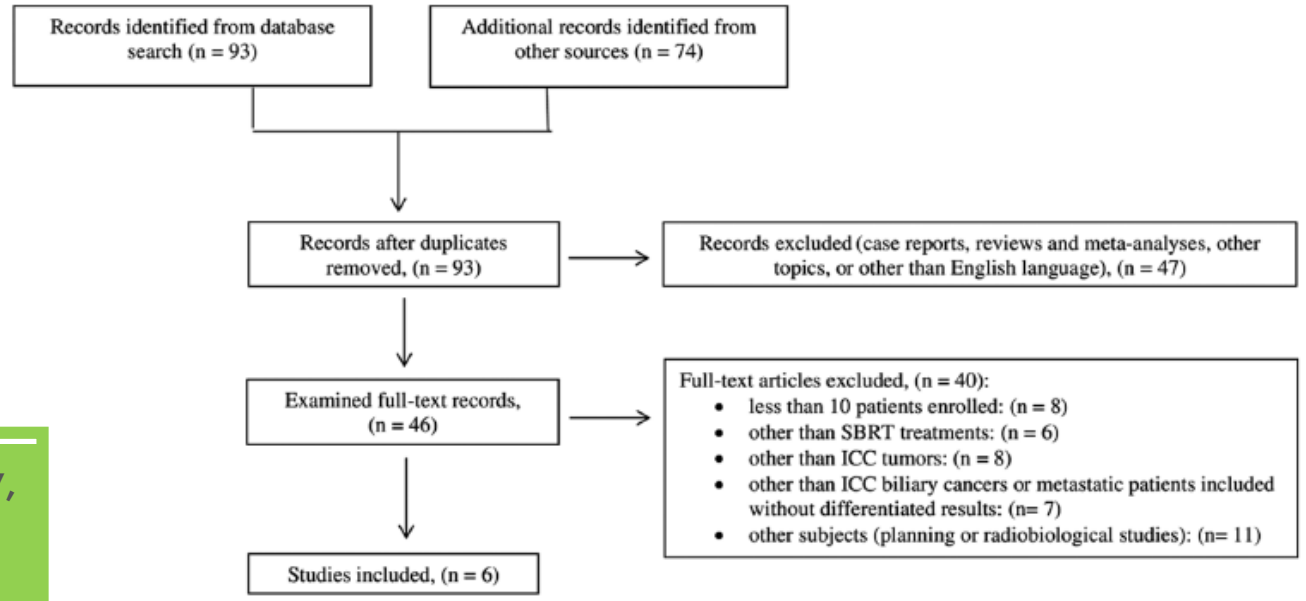
SILVIA BISELLO[1,2], ANNA CHIARA CAMILLETTI[1], FEDERICA BERTINI[1,2], MILLY BUWENGE[1,2], ALESSANDRA ARCELLI[1,2], GABRIELLA MACCHIA[3], FRANCESCO DEODATO[3], SAVINO CILLA[4], GIANCARLO MATTIUCCI[5], ROSA AUTORINO[5], GIOVANNI BRANDI[6], LIDIA STRIGARI[7], SILVIA CAMMELLI[1,2*] and ALESSIO G. MORGANTI[1,2*]

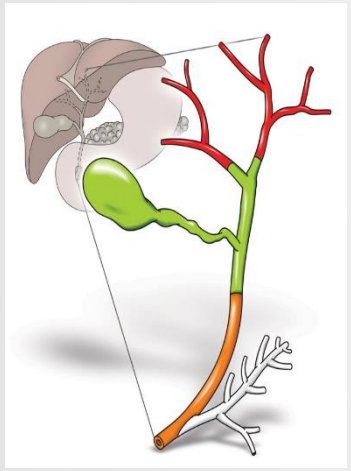
[1]Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna; [2]Radiation Oncology Center, Department of Experimental, Diagnostic, and Specialty Medicine, Alma Mater Studiorum Bologna University, I-40138 Bologna; [3]Radiotherapy Unit and [4]Medical Physic Unit, Gemelli Molise Hospital, Università Cattolica del Sacro Cuore, I-86100 Campobasso; [5]Fondazione Policlinico Universitario A. Gemelli IRCCS, UOC di Radioterapia, Dipartimento di Scienze Radiologiche, Radioterapiche ed Ematologiche, I-00168 Rome; [6]Department of Medical and Surgical Sciences, University of Bologna, S. Orsola-Malpighi Hospital; [7]Medical Physics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, I-40138 Bologna, Italy

Received November 21, 2020; Accepted April 1, 2021

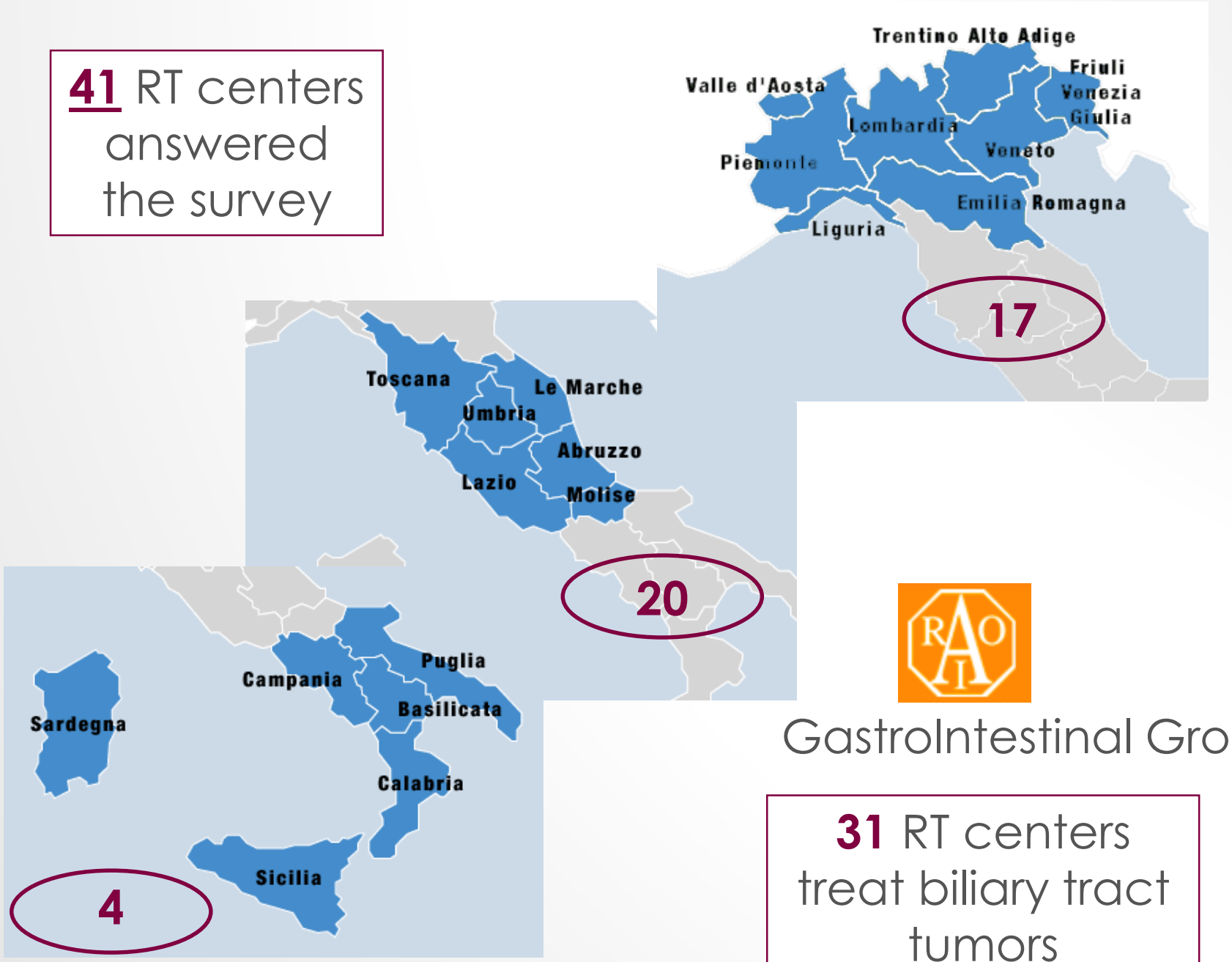
DOI: 10.3892/mco.2021.2314

MOLECULAR AND CLINICAL ONCOLOGY 15: 152, 2021



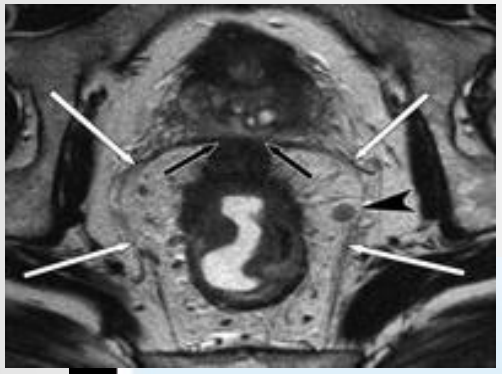


41 RT centers answered the survey



GastroIntestinal Group

31 RT centers treat biliary tract tumors

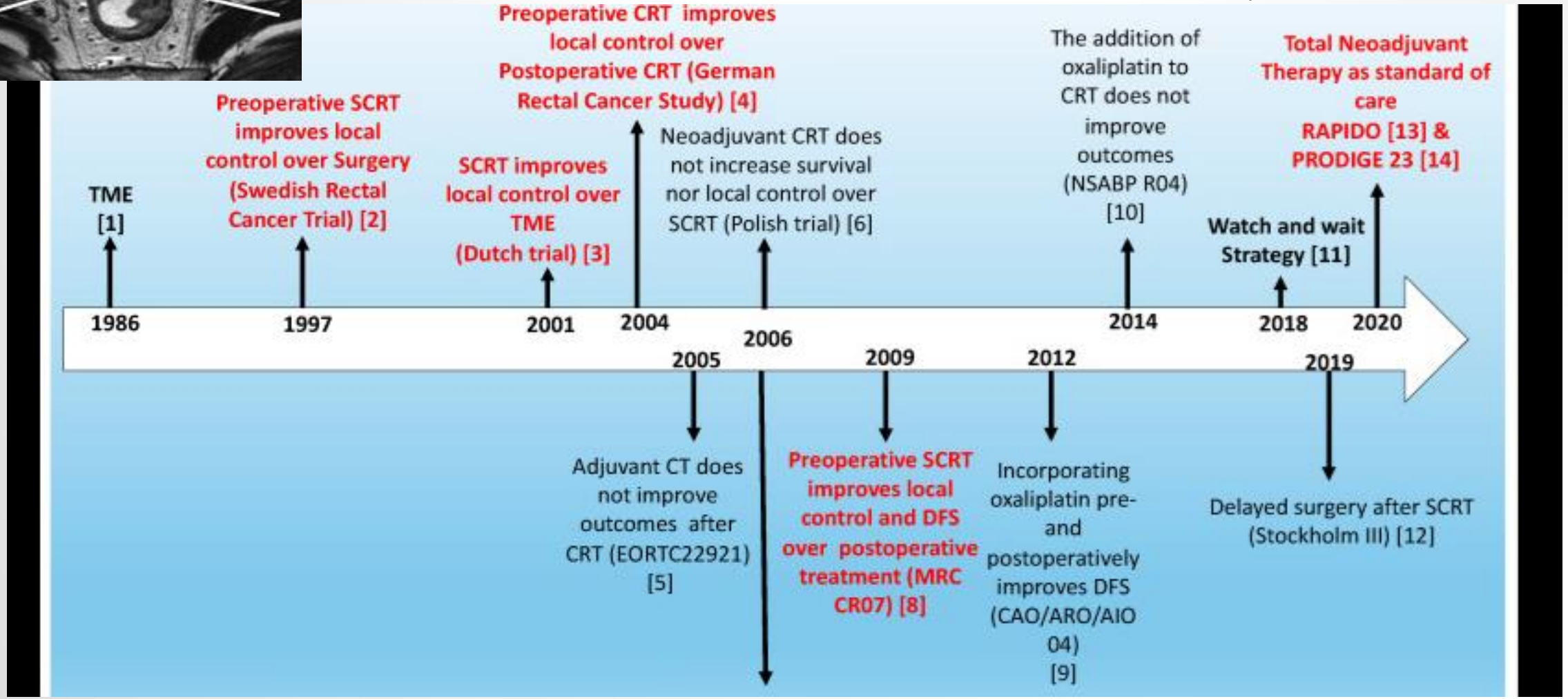


cancers

Review

Neoadjuvant Chemotherapy in Locally Advanced Rectal Cancer

Cancers **2020**, 12, 3611;



Fallimento terapeutico ripresa a distanza nel 25-30% pazienti con neoplasia localmente avanzata

Dati letteratura

- Correlazione dose RT-risposta

  Appelt 2013, Burbach 2014

- Fallimento oxaliplatino

  Rodel 2012, O'Connell 2014, Gerard 2012

- Ruolo prognostico pRC

  Capirci 2008, Maas 2010

- Ruolo RM

  Mercury Trial 2011, Barbaro 2012

Opzioni terapeutiche

- Intensificazione della radioterapia
- Intensificazione della chemioterapia
- Modifica dell'intervallo radioterapia-chirurgia
- Modifica approccio chirurgico ("Wait and watch policy" o escissione locale, TEM)

Radiotherapy and Oncology 134 (2019) 110–118

Contents lists available at ScienceDirect

Radiotherapy and Oncology

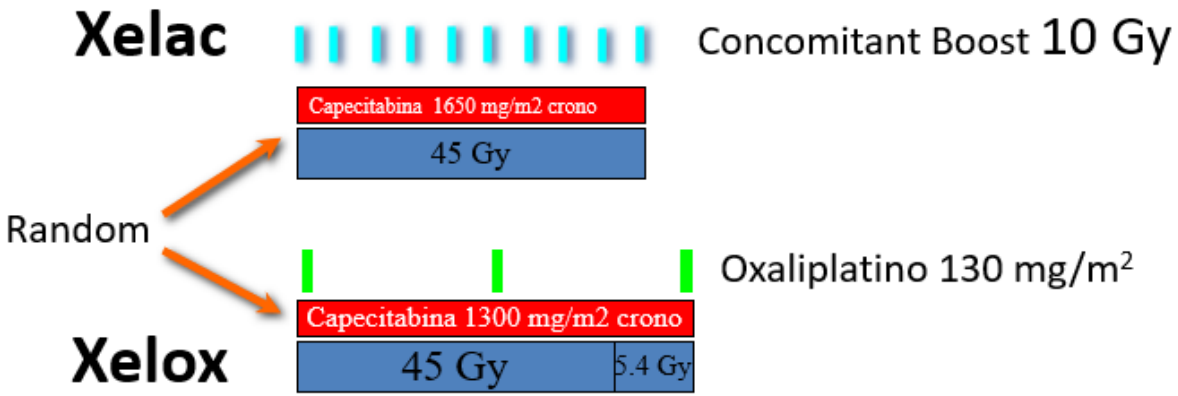
journal homepage: www.thegreenjournal.com

The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer

Vincenzo Valentini [a], Maria Antonietta Gambacorta [a], Francesco Cellini [b,*], Cynthia Aristei [c], Claudio Coco [d],

Braccio XELAC trattamento di riferimento

Studio INTERACT



Obiettivi.

Primario: valutazione risposta patologica

Secondario: tossicità, DFS e OS

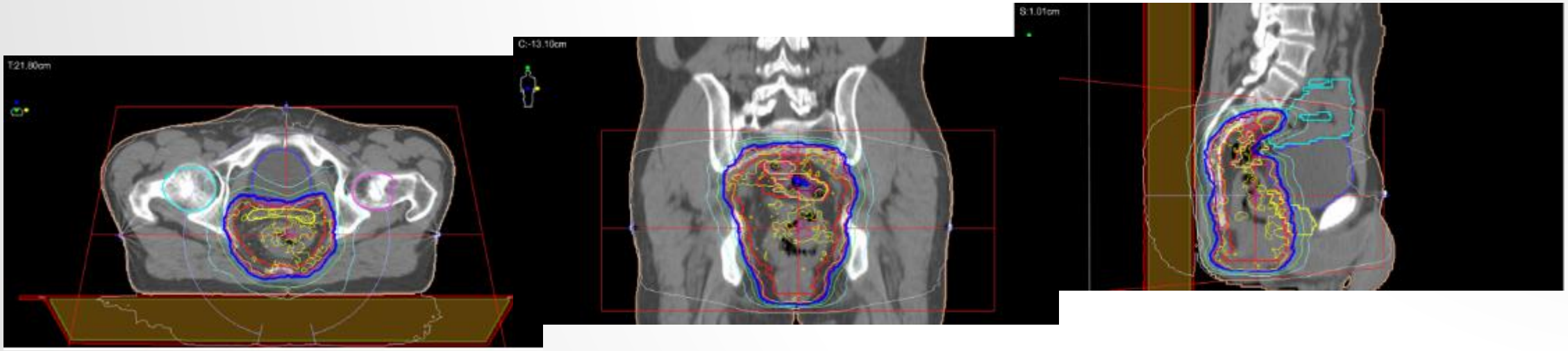
Casistica: 534 pz – cT3 N0-2, MRF +/-; cT2 N+ retto inferiore

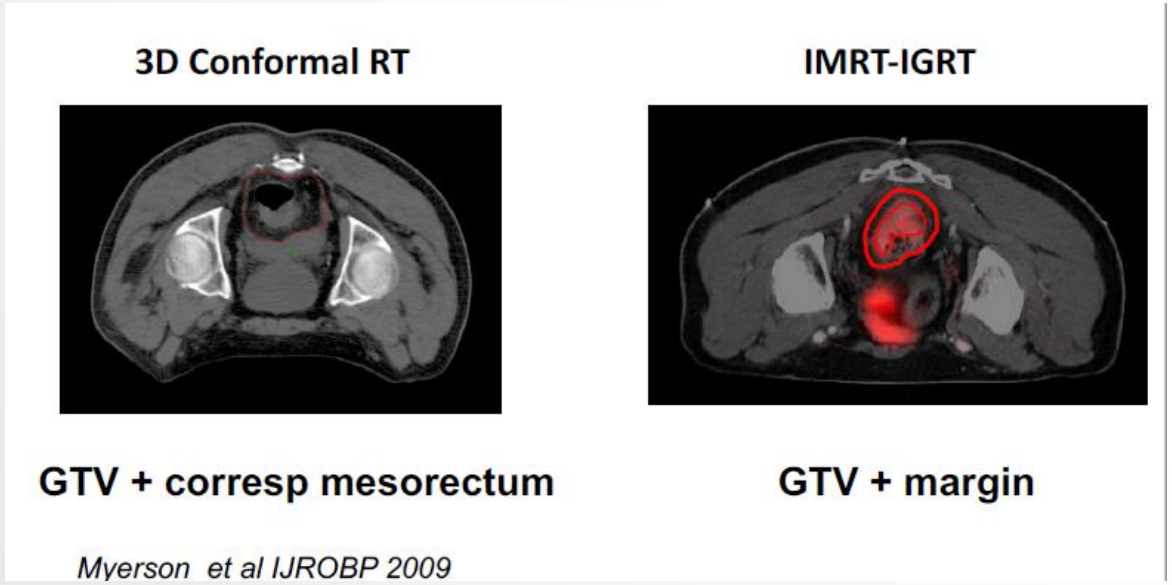
Studio INTERACT: risultati

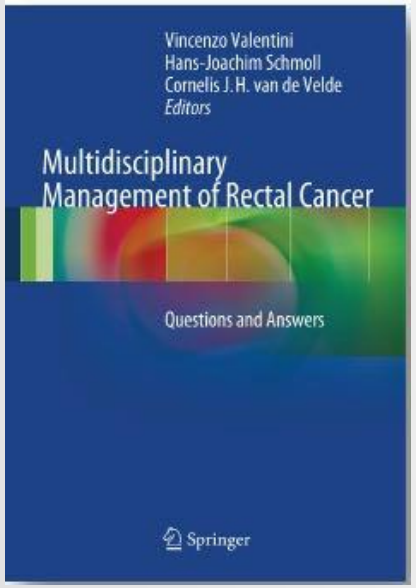
Variabile	XELAC	XELOX	p
TRG 1	32.3%	32.9%	NS
TRG 1-2	61.7%	52.3%	0.039
Compliance RT	95%	96.4%	NS
Compliance chemioterapia	91.8%	86.3% (81.9)	0.039
Tossicità ematologica ≥ 3			0.01
Tossicità GI ≥ 3	10.2	16.9	0.054
Tossicità neurologica ≥ 3	1.7	21.7	0.001
Controllo locale, DFS, OS			NS

TRG1 vs TRG 2-5 p<0.01 fattore prognostico per DFS e OS

INTENSIFICAZIONE RT





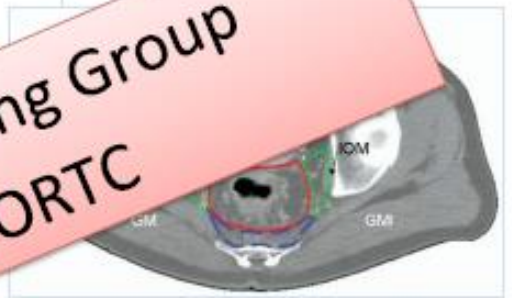


CLINICAL INVESTIGATION — **Rectum**

DEFINITION AND DELINEATION OF THE CLINICAL TARGET VOLUME FOR RECTAL CANCER

Sarah Roels, M.D.,* Wim Duthoy, M.D.,† Karin Haustermans, M.D., Ph.D.,* Freddy Penninckx, M.D., Ph.D.,† Vincent Vandecaveye, M.D.,‡ Tom Boterberg, M. and Wilfried De Neve, M.D., Ph.D.§

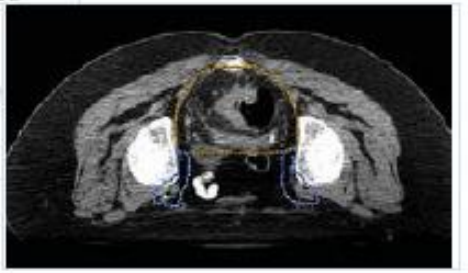
Departments of *Radiotherapy, †Surgery, and ‡Radiology, University Hospital Gasthuisberg, Le... Radiotherapy, Ghent University Hospital, Ghent, Bel...



CLINICAL INVES... — **Rectum**

...R CONFORMAL THERAPY IN ...RAPY ONCOLOGY GROUP CONSENSUS ...NTOURING ATLAS

..., Ph.D.,* Michael C. Garofalo, M.D.,† Issam El Naqa, Ph.D.,* ..., Aditya Apte, Ph.D.,* Walter R. Bosch, Ph.D.,* Prajnan Das, M.D., ... L. Gunderson, M.D.,‖ Theodore S. Hong, M.D.,¶ J. J. John Kim, M.D.,# Christopher G. Willett, M.D.,** and Lisa A. Kachnic, M.D.††



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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Rectal cancer guidelines

International consensus guidelines on Clinical Target Volume delineation in rectal cancer

Vincenzo Valentini [a], Maria Antonietta Gambacorta [a,*], Brunella Barbaro [b], Giuditta Chiloiro [a], Claudio Coco [c], Prajnan Das [d], Francesco Fanfani [e], Ines Joye [f], Lisa Kachnic [g], Philippe Maingon [h], Corrie Marijnen [i], Samuel Ngan [j], Karin Haustermans [f]

Guidelines 2016 - Join Working Group
ESTRO-ASTRO-TROG-EORTC

Radiotherapy and Oncology 161 (2021) 198–204

Contents lists available at ScienceDirect

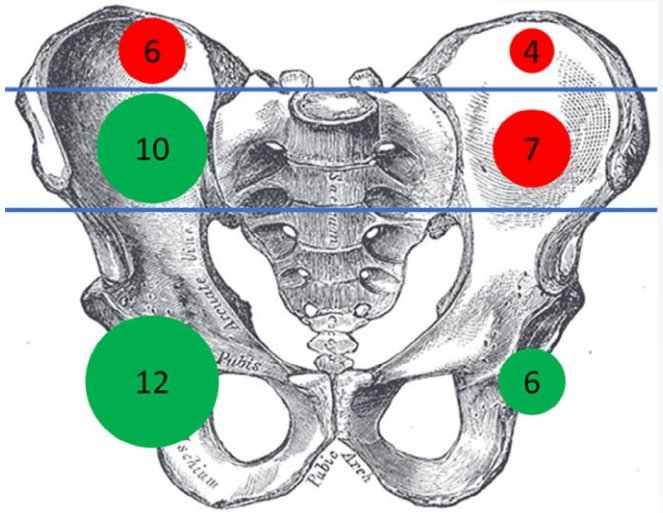
Radiotherapy and Oncology

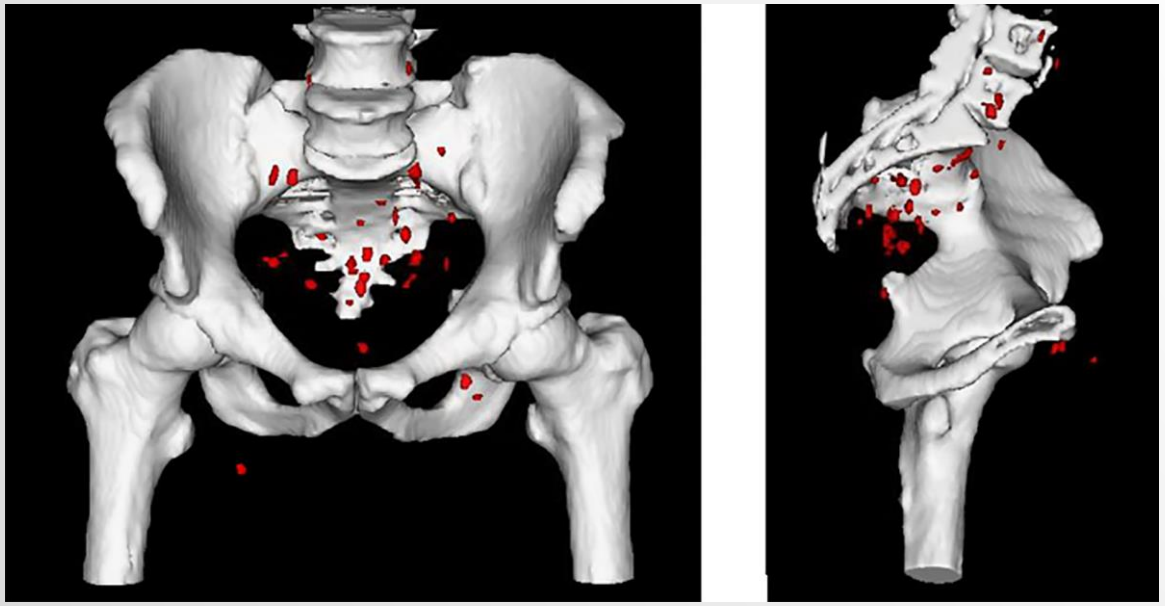
journal homepage: www.thegreenjournal.com

Original Article

Locoregional relapses in the ACCORD 12/0405-PRODIGE 02 study: Dosimetric study and risk factors ☆

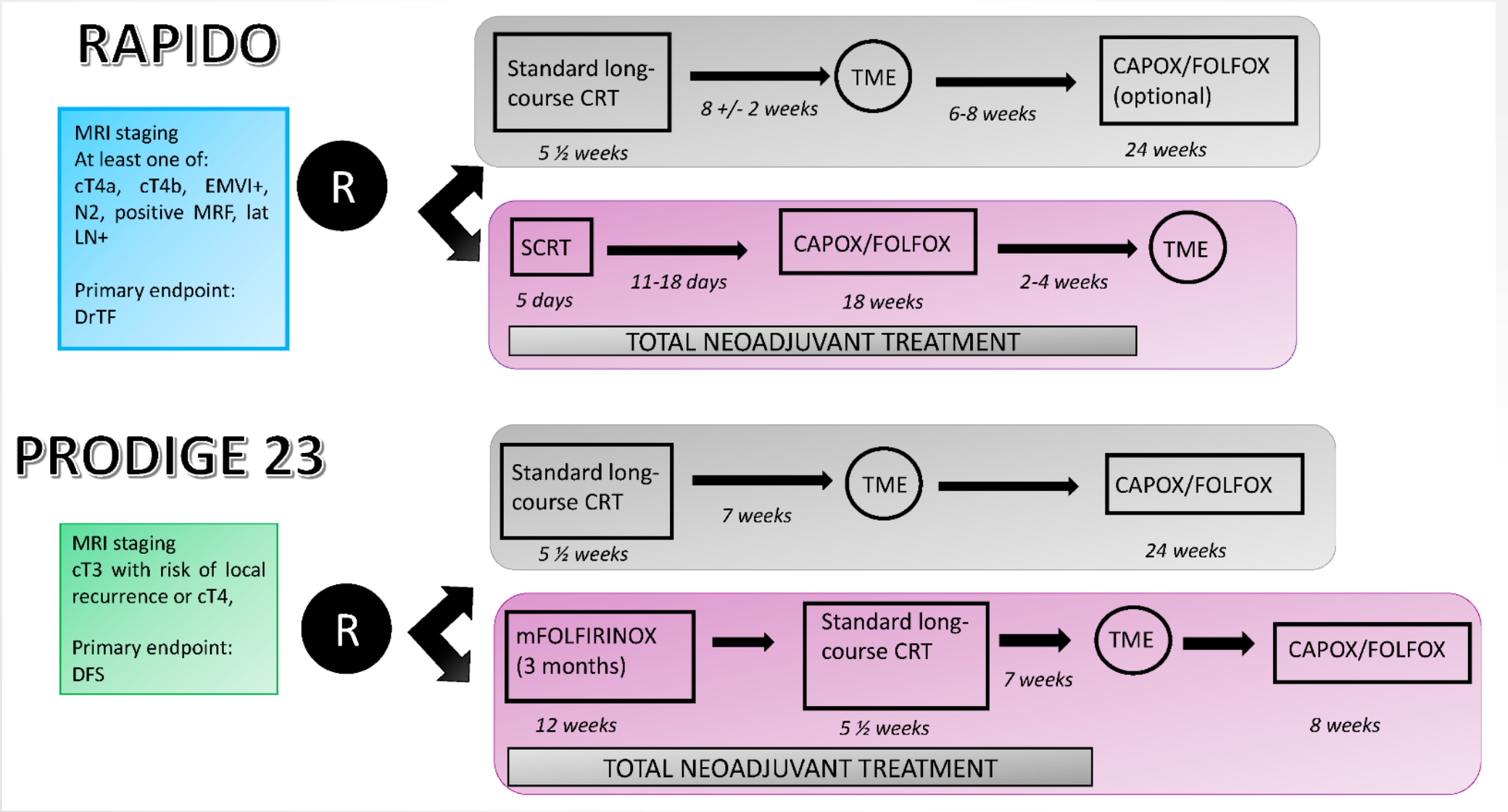
Nicolas Meillan [a,b,*], Alexandre Orthuon [c], Paul Chauchat [d], David Atlani [e], Olivier Bouche [f], Bertrand Chaulin [g], Céline David [h], Mélanie Deberne [i], Charles Debrigode [j], William Kao [k], Audrey Keller [l], Hortense Laharie [m], Bruno Lamezec [n], Claire Lemanski [o], Nicolas Magné [p], Marc-André Mahé [q], Pascale Mere [r], Laurence Moureau-Zabotto [s], Didier Peiffert [t], Yoann Pointreau [u], Laurent Quéro [v], Séverine Racadot [w], Sophie Roca [x], Paul Sargos [y], Stéphanie Servagi [z], Eliane Tang [ac], Véronique Vendrely [aa,ab], Jérôme Doyen [ad], Florence Huguet [b,ae,af]



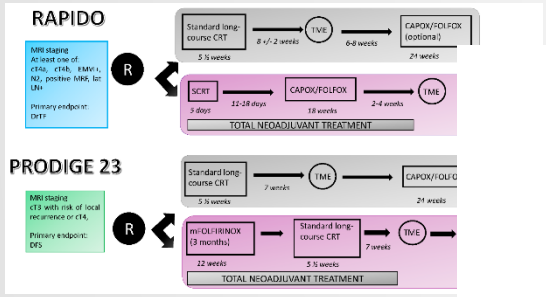


- Recidive locoregionali sono in field.
- - Nei tumori T4 o margine di resezione circonferenziale dubbio margine craniale a L5-S1
- - Nei tumori è corretta un'irradiazione nodale elettiva più estesa, in particolare includendo i nodi iliaci laterali ed esterni anteriori.

Lancet Oncol 2021; 22: 29–42

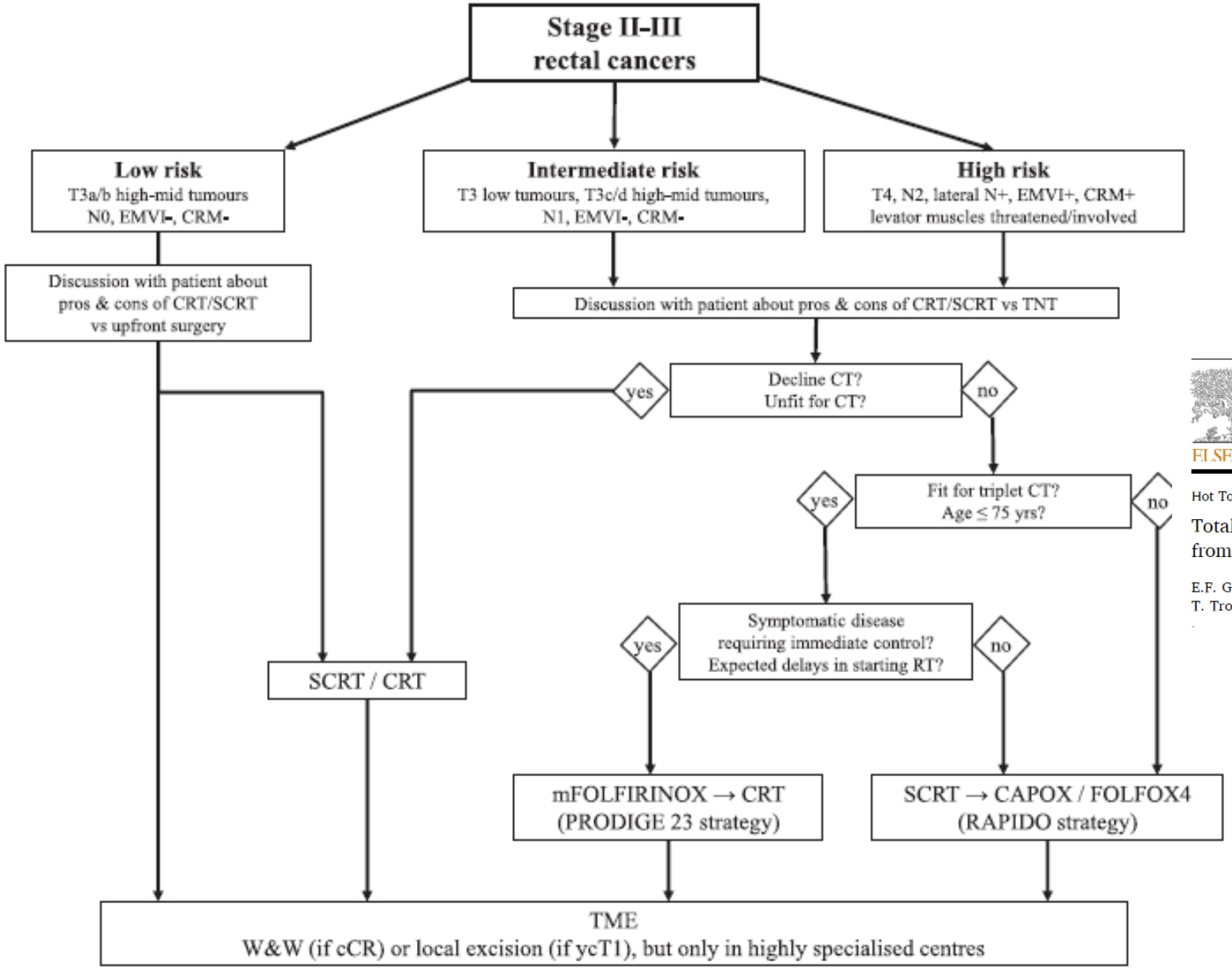


Lancet Oncol 2021; 22: 702–15



Patient Characteristics	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Median age	61 yrs vs. 61 yrs	61 yrs vs. 62 yrs
Patients enrolled	462 vs. 450	231 vs. 230
cT4 (%)	30.4% vs. 31.8%	17.8% vs. 15.6%
cN2 (%)	68% vs. 68%	Not stated
EMVI+ (%)	32% vs. 28%	Not stated
MRF involved	62% vs. 60%	26% vs. 27.7%

Outcomes	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Median FU	4.6 yrs	3.8 yrs
Primary endpoint	3-yrs DrTF	3-yrs DFS
	23.7% vs. 30.4% (HR 0.75 [95% CI 0.60–0.96]; $p = 0.019$)	75.7% vs. 68.5% (HR 0.69 95% [CI 0.49–0.97]; $p = 0.034$)
3-year MFS	80% vs. 73.2%	78.8% vs. 71.7%
pCR rate	28.4% vs. 14.3%	27.5% vs. 11.7%
Local relapse	8.7% vs. 5.4%	4.8% vs. 7%
3-year OS	89.1% vs. 88.8%	90.8% vs. 87.7%



Cancer Treatment Reviews 96 (2021) 102177

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Hot Topic

Total neoadjuvant therapy for rectal cancer: Making sense of the results from the RAPIDO and PRODIGE 23 trials

E.F. Giunta [a], G. Bregni [b], A. Pretta [b], A. Deleporte [b], G. Liberale [c], A.M. Bali [d], L. Moretti [e], T. Troiani [a], F. Ciardiello [a], A. Hendlisz [b], F. Sclafani [b,*]

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Original Research Article

Time to surgery and pathologic complete response after neoadjuvant chemoradiation in rectal cancer: A population study on 2094 patients

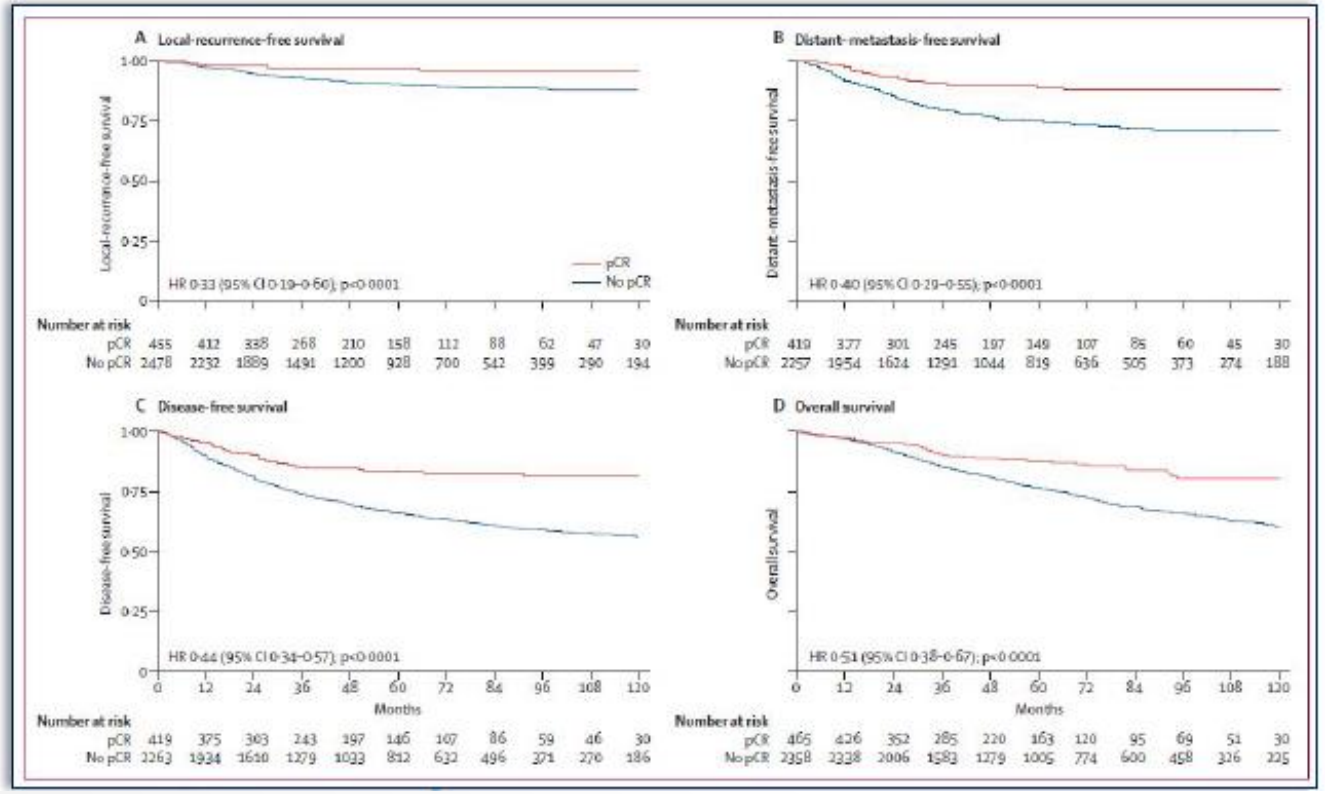
Gabriella Macchia [a,*], Maria Antonietta Gambacorta [b], Carlotta Masciocchi [b], Giuditta Chiloiro [b], Giovanna Mantello [c], Maika di Benedetto [c], Marco Lupattelli [d], Elisa Palazzari [d], Liliana Belgioia [e], Almalina Bacigalupo [e], Aldo Sainato [f], Sabrina Montrone [f], Lucia Turri [g], Angela Caroli [g], Antonino De Paoli [h], Fabio Matrone [h], Carlo Capirci [i], Giampaolo Montesi [i], Rita Marina Niespolo [j], Mattia Falchetto Osti [k], Luciana Caravatta [l], Alessandra Galardi [m], Domenico Genovesi [n], Maria Elena Rosetto [o], Caterina Boso [p], Piera Sciacero [q], Lucia Giaccherini [r], Salvatore Parisi [s], Antonella Fontana [t], Francesco Romeo Filippone [u], Vincenzo Picardi [a], Alessio Giuseppe Morganti [r,1], Vincenzo Valentini [b,1]

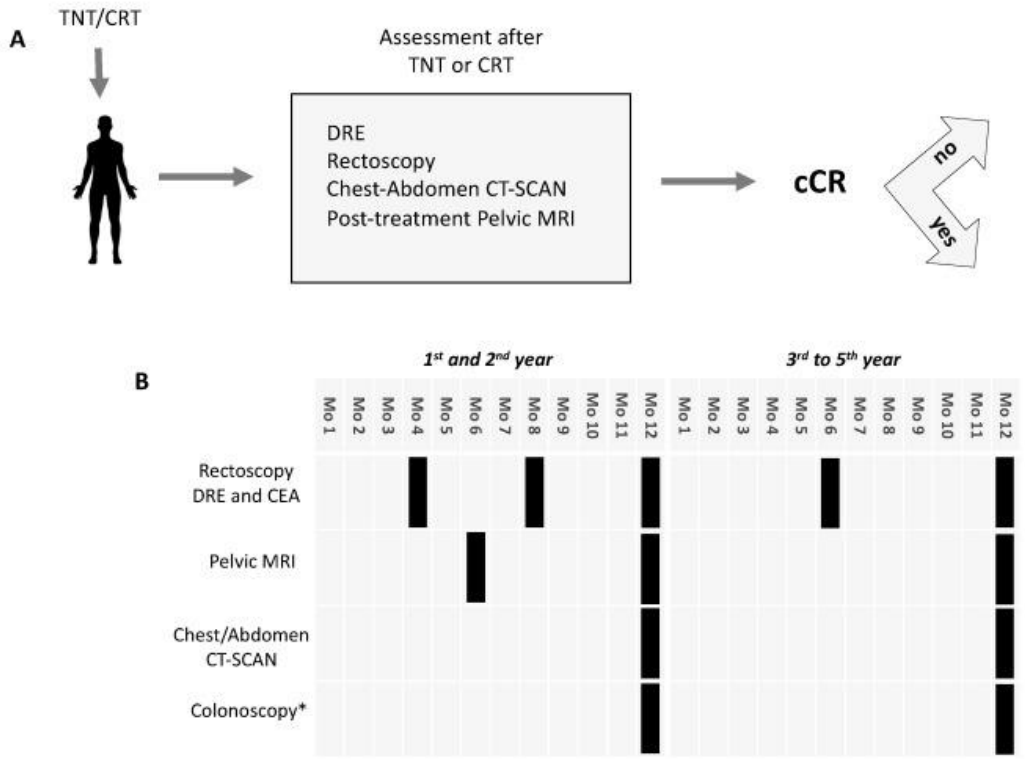
Time to surgery	pCR
≤ 6 weeks	12.6%
7-12 weeks	23%
> 12 weeks	31.8%

p < 0.001

OS

Maas M et al. Lancet Oncol 2010





cancers
MDPI
Review

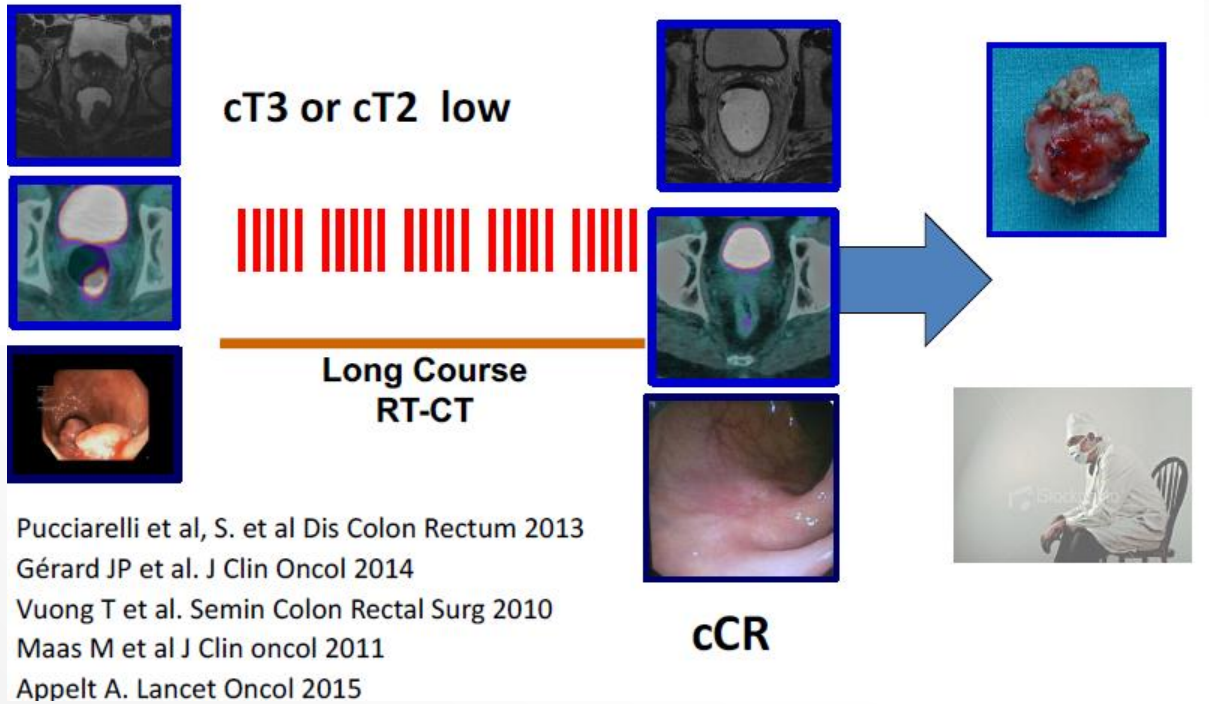
Neoadjuvant Chemotherapy in Locally Advanced Rectal Cancer

TME

Watch and Wait strategy

Cancers **2020**, 12, 3611;

Surgery descalation



Pucciarelli et al, S. et al Dis Colon Rectum 2013
Gérard JP et al. J Clin Oncol 2014
Vuong T et al. Semin Colon Rectal Surg 2010
Maas M et al J Clin oncol 2011
Appelt A. Lancet Oncol 2015

Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study

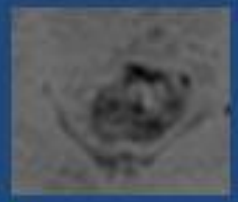
Laura M Fernandez, Guilherme P São Julião, Nuno L Figueiredo, Geerard L Beets, Maxime J M van der Valk, Renu R Bahadoer, Denise E Hilling, Elma Meershoek-Klein Kranenbarg, Annet G H Roodvoets, Andrew G Renehan, Cornelis J H van de Velde, Angelita Habr-Gama, Rodrigo O Perez, the International Watch & Wait Database Consortium*

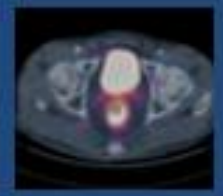
Lancet Oncol 2021; 22: 43–50

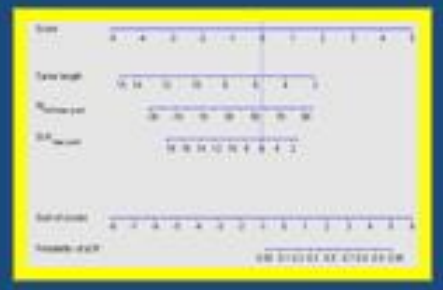
We identified 793 patients in the IWWD with clinical complete response who had been managed by a watch-and-wait strategy. Median follow-up was 55·2 months (IQR 36·0–75·6). The probability of remaining free from local regrowth for an additional 2 years if a patient had a sustained clinical complete response for 1 year was 88·1% (95% CI 85·8–90·9), for 3 years was 97·3% (95·2–98·6), and for 5 years was 98·6% (97·6–100·0). The probably of remaining free from distant metastasis for a further 2 years in patients who had a clinical complete response without distant metastasis for 1 year was 93·8% (92·3–95·9), for 3 years was 97·8% (96·6–99·3), and for 5 years was 96·6% (94·0–98·9).

Bridge Studies

PROSPETTIVE FUTURE







Low risk

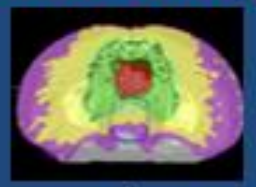
Intermed risk

High risk

Surgery descalation

RT intesification
+/- 1 drug

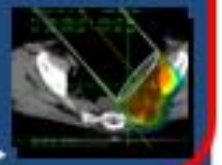
CT-RT intesification

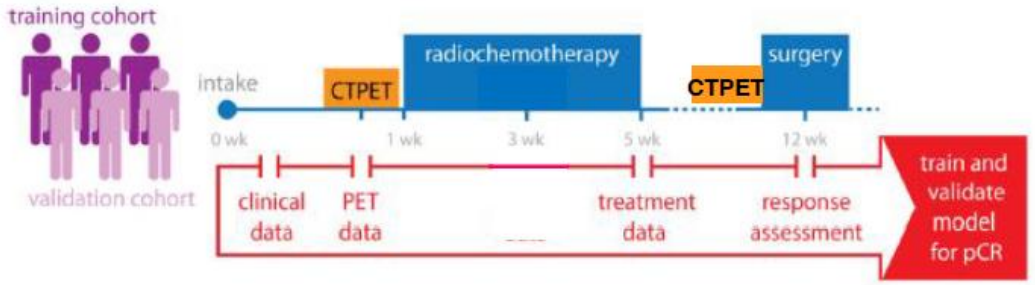


2 drugs
+/- biol

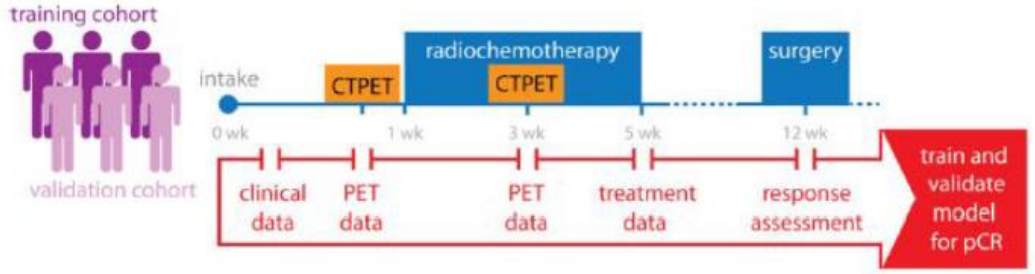
1 drug

S +/-
IORT



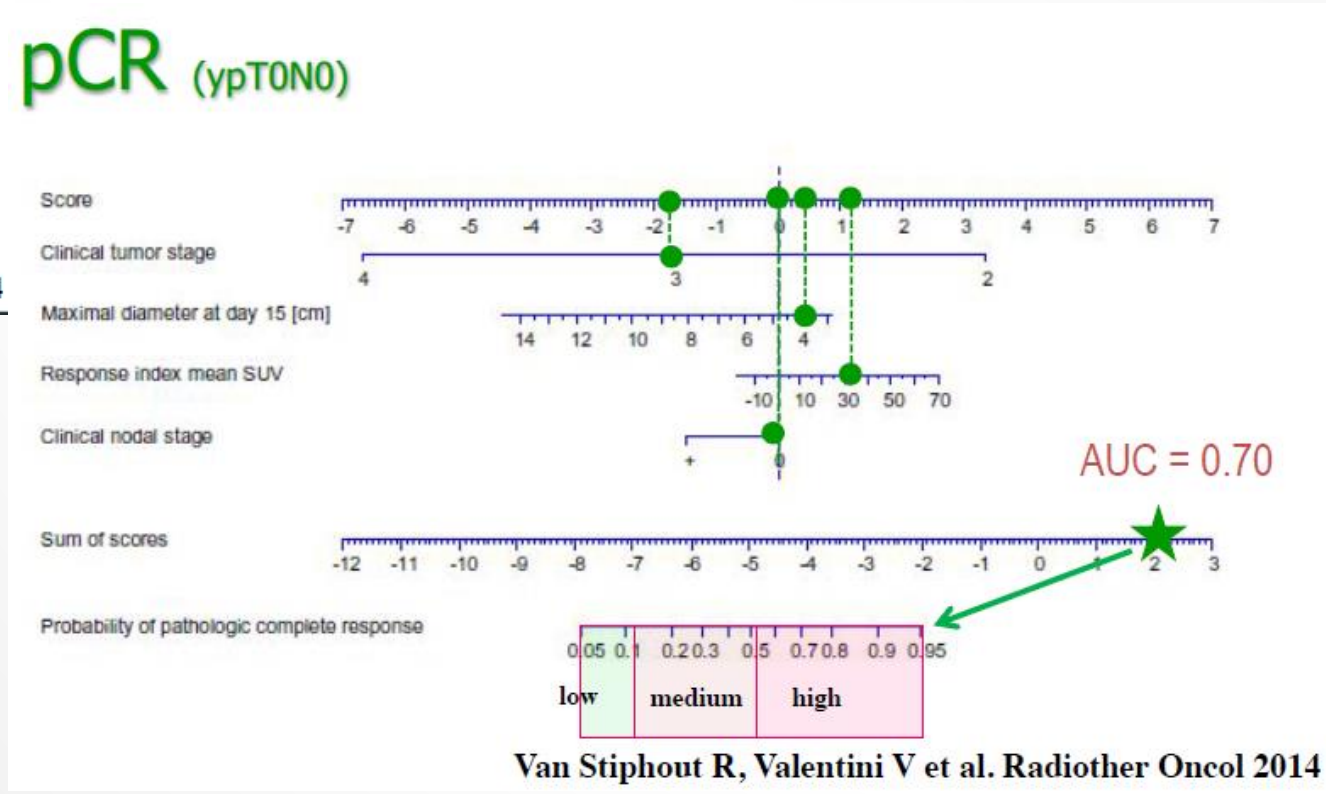


Van Stiphout R, Valentini V et al. Radiother Oncol 2011



Van Stiphout R, Valntini V. et al. Radiother Oncol 2014

NOMOGRAMMI



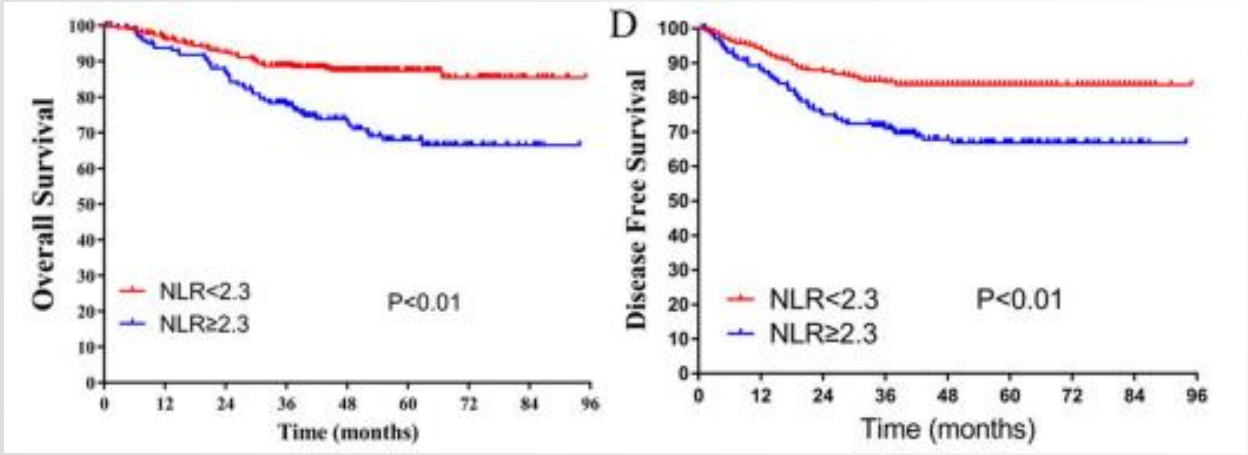
Van Stiphout R, Valentini V et al. Radiother Oncol 2014

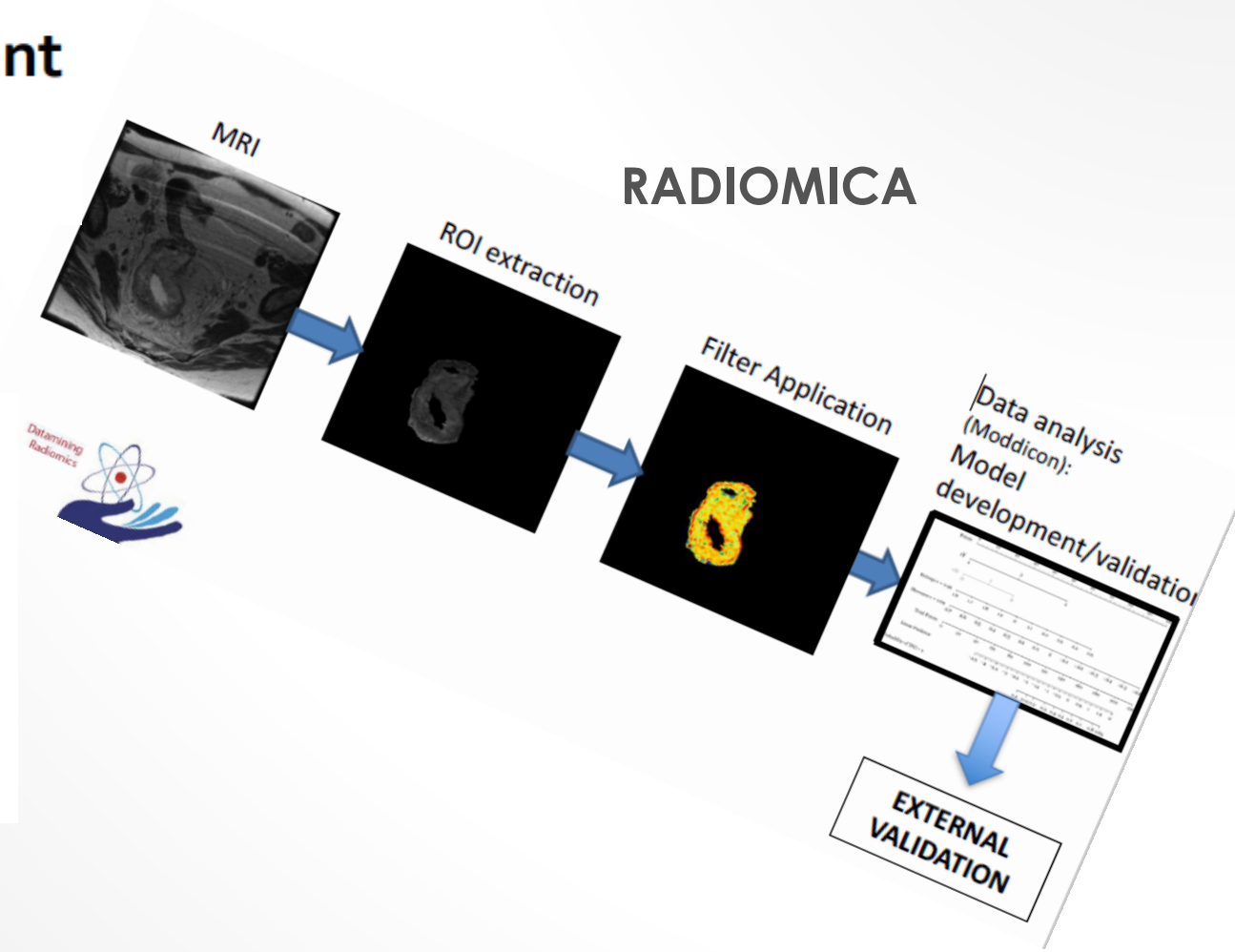
OPEN

Prognostic value of pretreatment systemic inflammatory markers in patients with locally advanced rectal cancer following neoadjuvant chemoradiotherapy

Yiyi Zhang[1,5], Xing Liu[2,5], Meifang Xu[3,5], Kui Chen[4], Shoufeng Li[1] & Guoxian Guan[1]✉

Scientific Reports | (2020) 10:8017





TRATTAMENTO DELLE FORME INFILTRANTI : MARGINE ANALE

cute entro un raggio di 5 cm intorno all'ano : cute perianale

STADIO I G1/2

OS a 5 anni 88%

- ESCISSIONE LOCALE

Margini adeguati (5mm-1 cm) → Osservazione

Margini inadeguati → Reiscissione

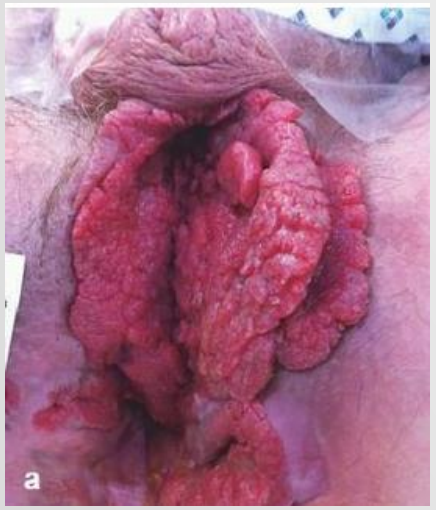
RT +/- CT

STADIO I G3

- ESCISSIONE LOCALE
- RT + CT

STADIO II-III

- RT+CT



TRATTAMENTO DELLE FORME INFILTRANTI : CANALE ANALE

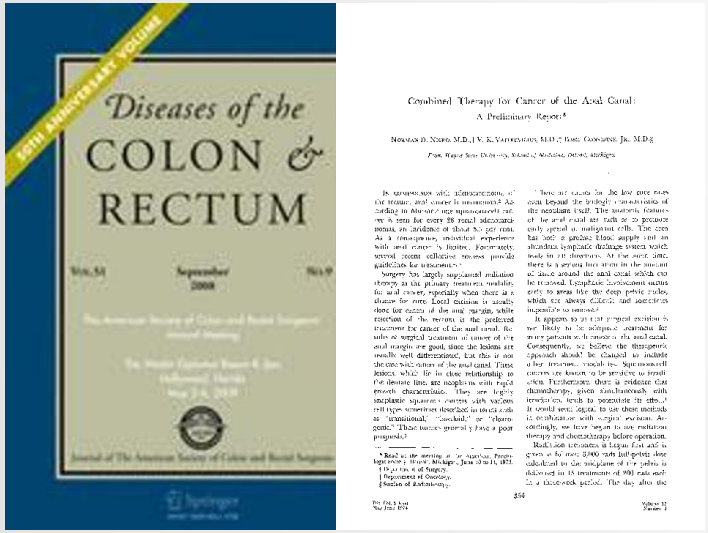
STADIO I

RT+ CT

RT esclusiva
(altro trattamento depotenziato)

STADIO II-III

- RT+CT



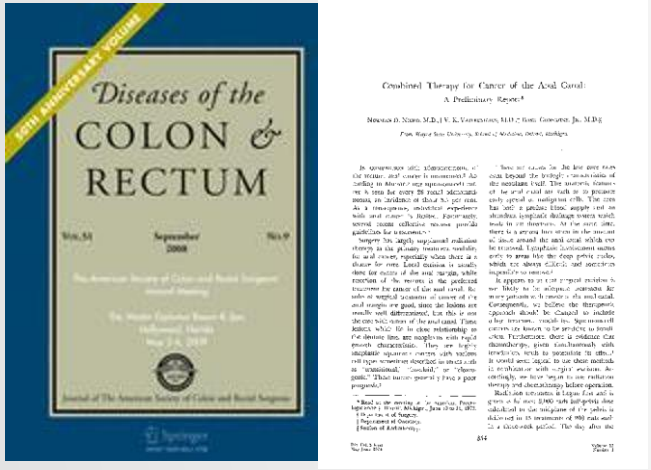
Nigro ND et al. Dis Colon Rectum 1974

RADIOCHEMIOTERAPIA DOPO NIGRO

TRIAL	STADIO	CT CONCOMITANTE	DOSE ERT	CT NEOADIUVANTE	CT ADIUVANTE
ACT 1 Northover et al. 96-2010	Qualsiasi tranne T1 (escissione locale)	☺	✗	✗	✗
RTOG 87-04 Flam et al. 1996	Ogni T, ogni N	☺	✗	✗	✗
EORTC 22861 Bartelink et al. 1997	T3/4N0-3 e T1-2 N1-3	☺	✗	✗	✗
RTOG 98-11 Ajani et al. 2008	T2-4, ogni N	☺	✗	☺	✗
ACCORD -03 Peiffert et al. 2012	Esclusi T1/T2,N0	✗	☺	☺	✗
UKCCCR ACT II James et al. 2013	Ogni T, ogni N	☺	✗	✗	☺

FU.MI.R

STANDARD OF CARE: ORGAN PRESERVATION IN PATIENTS WITH ANAL CARCINOMA WITH COMPLETE CLINICAL RESPONSE TO CT-RT

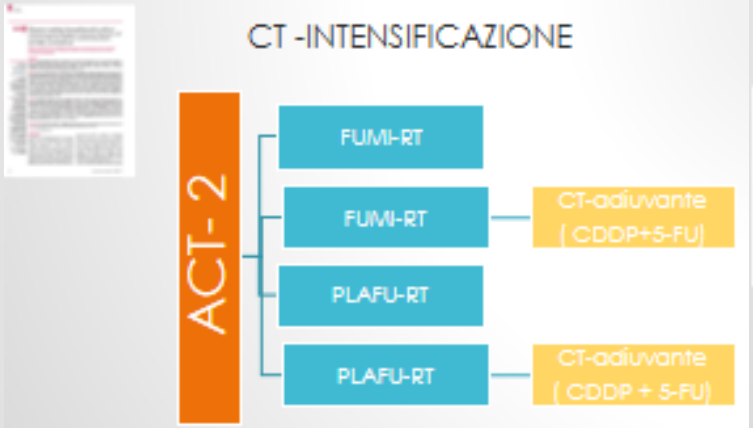


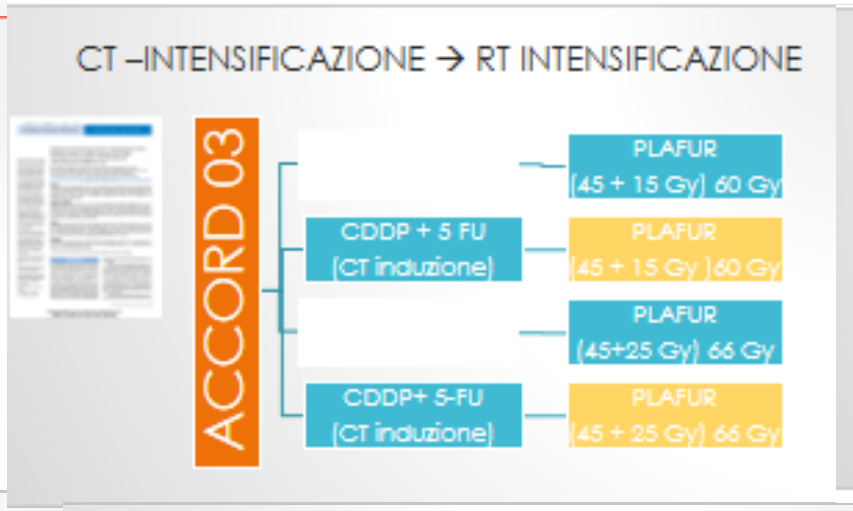
RT VS CRT

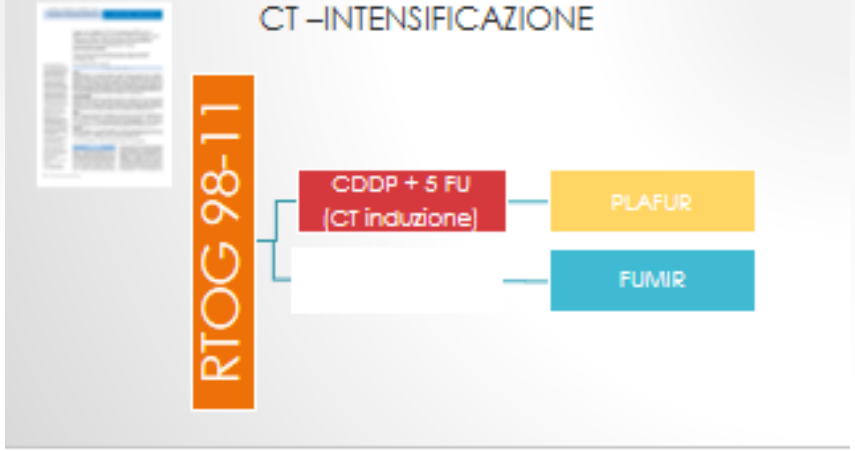
Nigro ND et al. Dis Colon Rectum 1974

TRIAL	TRATTAMENTO	LF %	CFS%	OS%
ACT 1 Northover et al. 96-2010 Qualsiasi tranne T1 (escissione locale)	FUMI-RT	36	72	65
	RT	59 (p=0,001)	61 (p=0,02)	68 (p=0,008)
RTOG 87-04 Flam et al. 1996 Ogni T, ogni N	FUMI-RT	17	71	78
	RT	36 (p=0.001)	59 (p=0,014)	71 (p=ns)
EORTC 22861 Bartelink et al. 1997 T3/4N0-3 e T1-2 N1-3	FUMI-RT	15	72	72
	RT	25 (p=0.02)	40 (p=0,02)	65 (p=0,014)

CT INTENSIFICAZIONE VS RT INTENSIFICAZIONE







CT-INTENSIFICAZIONE : ACT -2

CDDP VS MITOMICINA C

TRIAL	TRATTAMENTO	LF %	DFS%
UKCCCR ACT II James et al. 2013 Ogni T, ogni N	FUMIR	11	73
	PLAFUR	13	73

CT ADIUVANTE VS NON CT ADIUVANTE

TRIAL	TRATTAMENTO	Colostomia %	OS%
UKCCCR ACT II James et al. 2013 Ogni T, ogni N	NO CT ADIUVANTE	4	84
	CT ADIUVANTE	3	85

CT –INTENSIFICAZIONE → RT INTENSIFICAZIONE : ACCORD 03

TRIAL	TRATTAMENTO	LF %	CFS% 3anni	LC%	DFS%	OS%
ACCORD -03 Peiffert et al. 2012 Rectal T1/T2,N0	CT NEO+RT	28	83	88	70	79
	CT NEO+ HDRT	21	85	80	78	88.5
	CRT 60 Gy	30	86	90	67	89
	CRT HDRT 66 Gy	30	80	87	65	79

CT –INTENSIFICAZIONE : RTOG 98-11

TRIAL	TRATTAMENTO	LR % 5 anni	DF% 5 anni	% Colostomie 5 anni	DFS% 5 anni	OS% 5 anni
RTOG 98-11 Ajani et al. 2008 T2-4, ogni N	FUMIR	25	15	10	60	75
	CDDP -5FU + PLAFUR	33 p=0.07	19	19 p=0.02	54	70

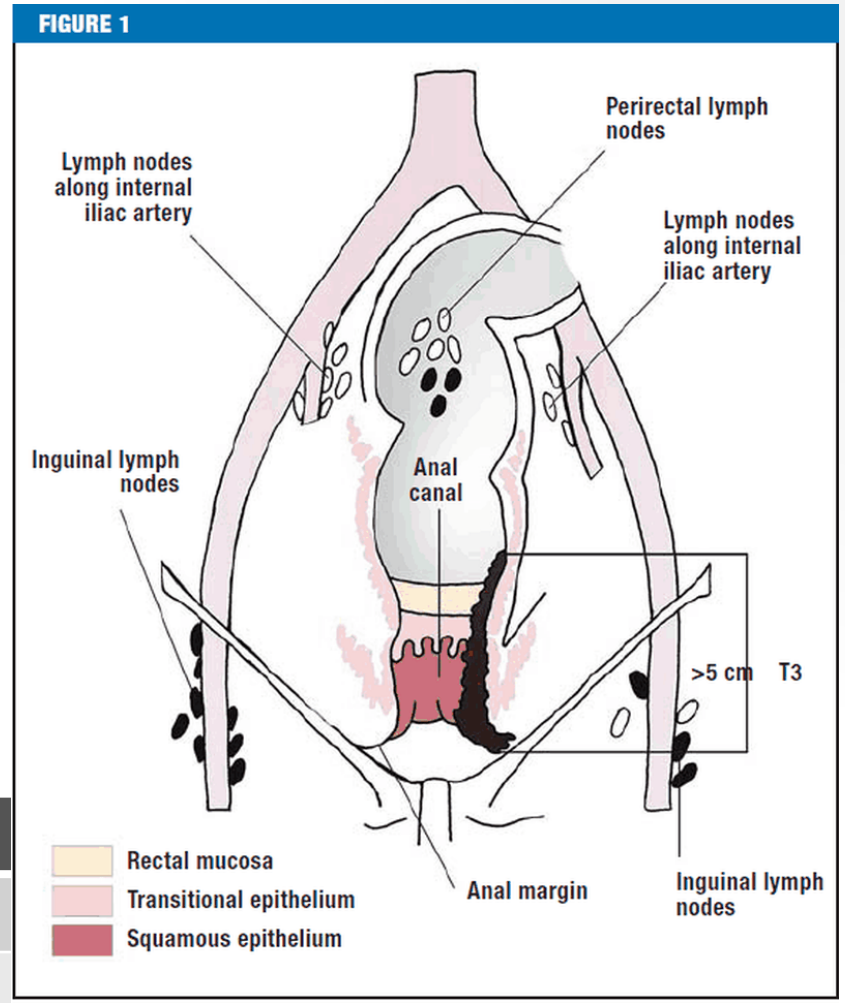
FU.MI.R

STANDARD OF CARE: ORGAN PRESERVATION IN PATIENTS WITH ANAL CARCINOMA WITH COMPLETE CLINICAL RESPONSE TO CT-RT

CONTORNAZIONE / MODULAZIONE

- Alla presentazione :
  - Rischio di interessamento linfonodale alla diagnosi : 25%
  - Dopo APR : 1) LN+ pelvici → 30%; 2) LN+ inguinali 15-30%
  - Se clinicamente negativi: 10-15% mestastasi occulte nei LN inguinali
- Metastasi viscerali : 5-10%

OUTCOMES a 5 anni (RT, 5-FU,Mitomicina)			
STADIO	OS	LC	Sfintere
T1	80%	90-100%	
T2	70%	65-75%	
T3-4	50%	40-55%	
OVERALL	65-75%	60%	70%



Anatomy and lymph drainage of the anal region (7)
(from: Becker HD, Hohenberger W, Junginger T, Schlag PM. Tumoren der Analregion. In: Chirurgische Onkologie. Stuttgart, New York. Thieme 2002. Reproduced with the kind permission of Thieme publishers)

PATTERNS DI POSSIBILI RECIDIVE

SEDE DELLA RECIDIVA	%
RECIDIVA LOCALE	56
RECIDIVA LOCALE E REGIONALE (N)	22
RECIDIVA REGIONALE (N)	22

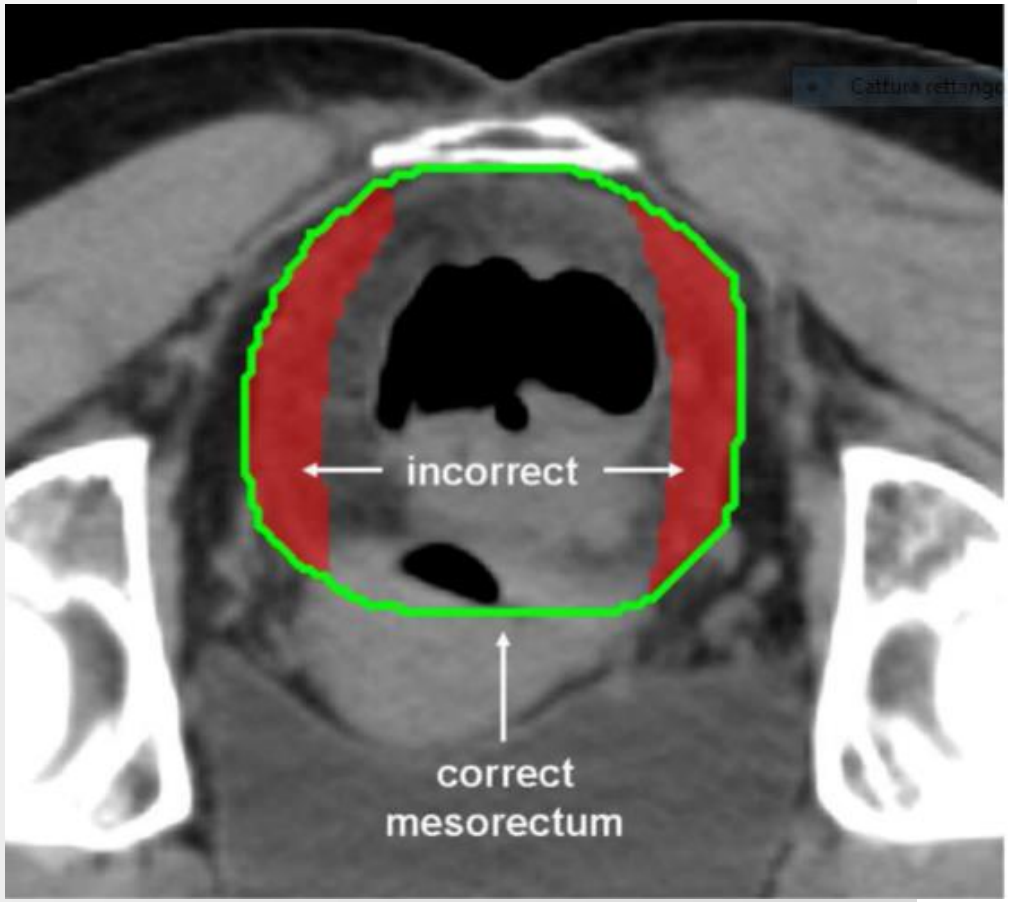
Wright J. et al. Int. J. Radiat. Oncol. Biol. Phys 2010

SEDE DELLA RECIDIVA	%
ANO/RETTO	75
N PRESACRALE/ ILIACO	21
N ILIACO	4

Das P. et al . Int. J. Radiat. Oncol. Biol. Phys 2007

RTOG 0529: A Phase II Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination with 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal

Lisa A. Kachnic et al. Int J Radiat Oncol Biol Phys . 2013 May 1; 86(1): 27–33

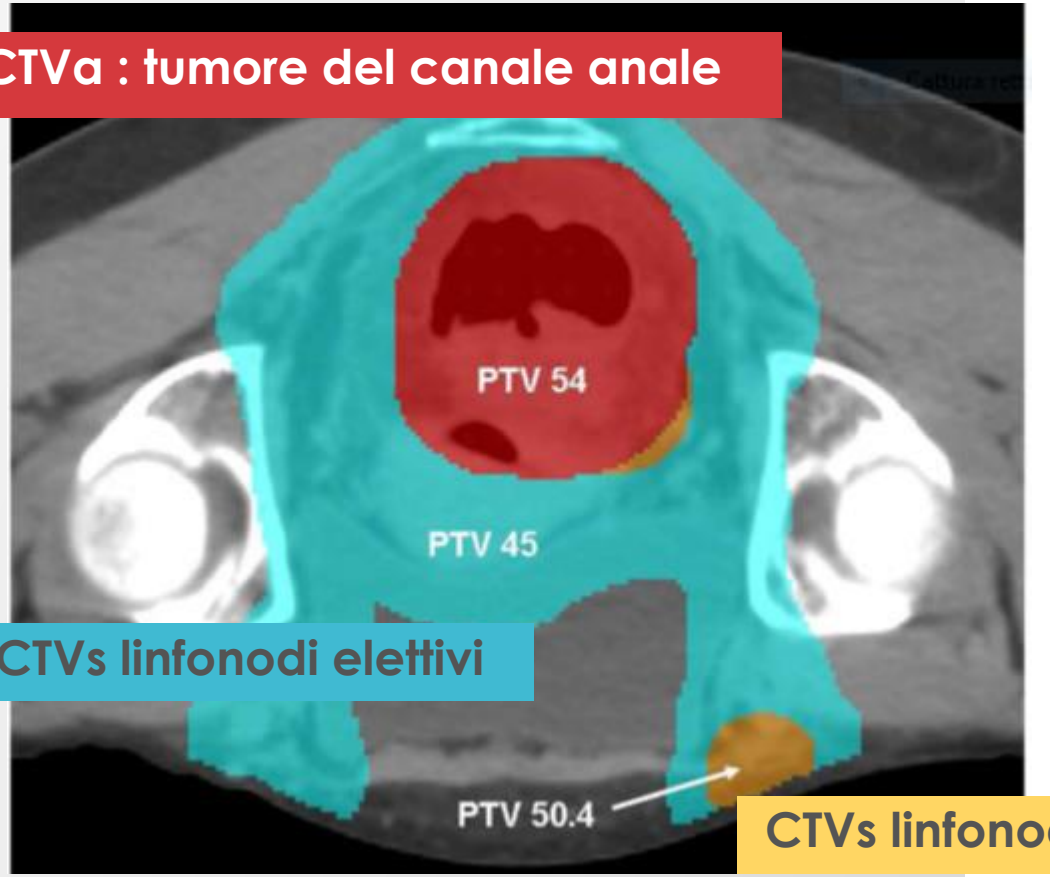


	CONTOURING NON CORRETTO (81%)	
GTV		21%
CTV elettivo		
	N mesoretto	55%
	N presacrale	43%
	N inguinale	33%
	N iliaci	31%

Intestino tenue	**60%**
Intestino crasso	**45%**

RTOG 0529: A Phase II Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination with 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal

Lisa A. Kachnic et al. Int J Radiat Oncol Biol Phys . 2013 May 1; 86(1): 27–33



VOLUME	DOSE TOTALE	DOSE FRAZIONE	NUMERO FRAZIONI	SETTIMANE
CTV-T	54 Gy	1.8 Gy	30	5
CTV N0	45 Gy	1.5 Gy	30	5
CTV N+ < 3 cm	50.4 Gy	1.68 Gy	30	5
CTV N+ > 3 cm	54 Gy	1,8 Gy	30	5

G3- GI /GU	P=< 0,0001

VALUTAZIONE RISPOSTA DOPO CRT

Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a post-hoc analysis of randomised controlled phase 3 trial

Robert Glynne-Jones, David Sebag-Montefiore, Helen M Meadows, David Cunningham, Rubina Begum, Fawzi Adab, Kim Benstead, Robert J Harte, Jill Stewart, Sandy Beare, Allan Hackshaw, Lathia Kadalayil, on behalf of the ACT II study group

Summary

Background Guidelines for anal cancer recommend assessment of response at 6–12 weeks after starting treatment. Using data from the ACT II trial, we determined the optimum timepoint to assess clinical tumour response after chemoradiotherapy.

Methods The previously reported ACT II trial was a phase 3 randomised trial of patients of any age with newly diagnosed, histologically confirmed, squamous cell carcinoma of the anus without metastatic disease from 59 centres in the UK. We randomly assigned patients (by minimisation) to receive either intravenous mitomycin (one dose of 12 mg/m² on day 1) or intravenous cisplatin (one dose of 60 mg/m² on days 1 and 29), with intravenous fluorouracil (one dose of 1000 mg/m² per day on days 1–4 and 29–32) and radiotherapy (50·4 Gy in 28 daily fractions); and also did a second randomisation after initial therapy to maintenance chemotherapy (fluorouracil and cisplatin) or no maintenance chemotherapy. The primary outcome was complete clinical response (the absence of primary and nodal tumour by clinical examination), in addition to overall survival and progression-free survival from time of randomisation. In this post-hoc analysis, we analysed complete clinical response at three timepoints: 11 weeks from the start of chemoradiotherapy (assessment 1), 18 weeks from the start of chemoradiotherapy (assessment 2), and 26 weeks from the start of chemoradiotherapy (assessment 3) as well as the overall and progression-free survival estimates of patients with complete clinical response or without complete clinical response at each assessment. We analysed both the overall trial population and a subgroup of patients who had attended each of the three assessments by modified intention-to-treat. This study is registered at controlled-trials.com, ISRCTN 26715889.

Findings We enrolled 940 patients from June 4, 2001, until Dec 16, 2008. Complete clinical response was achieved in 492 (52%) of 940 patients at assessment 1 (11 weeks), 665 (71%) of patients at assessment 2 (18 weeks), and 730 (78%) of patients at assessment 3 (26 weeks). 691 patients attended all three assessments and in this subgroup, complete clinical response was reported in 441 (64%) patients at assessment 1, 556 (80%) at assessment 2, and 590 (85%) at assessments 3. 151 (72%) of the 209 patients who had not had a complete clinical response at assessment 1 had a complete clinical response by assessment 3. In the overall trial population of 940 patients, 5 year overall survival in patients who had a clinical response at assessments 1, 2, 3 was 83% (95% CI 79–86), 84% (81–87), and 87% (84–89), respectively and was 72% (66–78), 59% (49–67), and 46% (37–55) for patients who did not have a complete clinical response at assessments 1, 2, 3, respectively. In the subgroup of 691 patients, 5 year overall survival in patients who had a clinical response at assessment 1, 2, 3 was 85% (81–88), 86% (82–88), and 87% (84–90), respectively, and was 75% (68–80), 61% (50–70), and 48% (36–58) for patients who did not have a complete clinical response at assessment 1, 2, 3, respectively. Similarly, progression-free survival in both the overall trial population and the subgroup was longer in patients who had a complete clinical response, compared with patients who did not have a complete clinical response, at all three assessments.

Interpretation Many patients who do not have a complete clinical response when assessed at 11 weeks after commencing chemoradiotherapy do in fact respond by 26 weeks, and the earlier assessment could lead to some patients having unnecessary surgery. Our data suggests that the optimum time for assessment of complete clinical response after chemoradiotherapy for patients with squamous cell carcinoma of the anus is 26 weeks from starting chemoradiotherapy. We suggest that guidelines should be revised to indicate that later assessment is acceptable.

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See Comment page 276

Mount Vernon Centre for Cancer Treatment, Northwood (R Glynne-Jones FRCR); University of Leeds, Leeds Cancer Centre, Leeds, UK (Prof D Sebag-Montefiore FRCR); Cancer Research UK and University College London Cancer Trials Centre, London, UK (HM Meadows MSc, R Begum BSc, S Beare PhD, Prof A Hackshaw MSc); Royal Marsden Hospital, London, UK (Prof D Cunningham MD); North Staffordshire Royal Infirmary, Stoke, UK (F Adab FRCR); Cheltenham General Hospital, Cheltenham, UK (K Benstead MD); Belfast City Hospital Cancer Centre, Belfast, UK (RJ Harte MD); Northampton General Hospital, Northampton, UK (J Stewart FRCR); and Faculty of Natural and Environmental Sciences, University of Southampton, Southampton, UK (L Kadalayil PhD)

Correspondence to Dr Robert Glynne-Jones, Mount Vernon Hospital, Rickmansworth Road, Northwood, HA6 2RN, UK rob.glynnejones@nhs.net

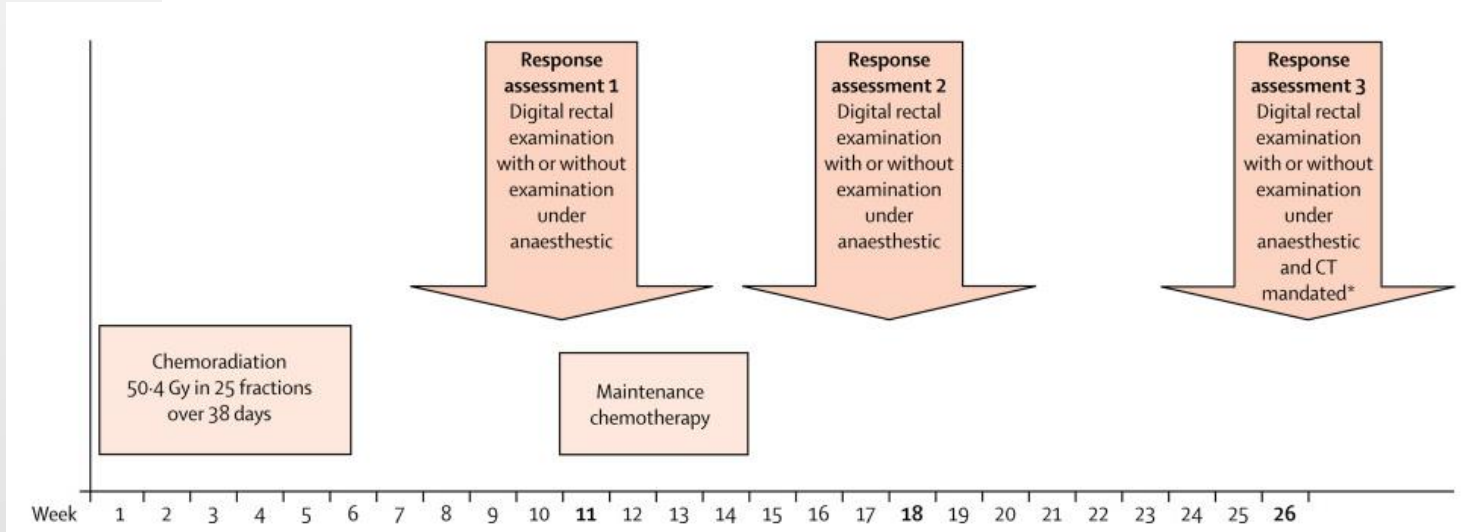
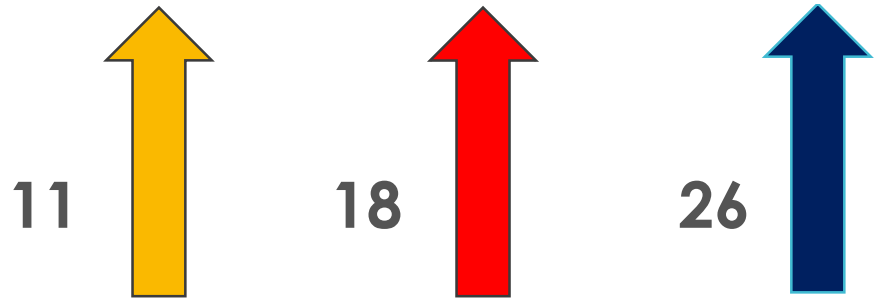


Figure 1 Treatment and assessment schedule in ACT II



R. Glynne-Jones (2017), Lancet Oncol.

151 (72%) di 209 pazienti non in risposta completa a 4 settimane dopo CRT , lo erano alla 26 settimana.

RACCOMANDAZIONI

- IN FASE DI STADIAZIONE LA BIOPSIA NON DEVE ESSERE PRESA IN CONSIDERAZIONE TRA GLI ESAMI DI ROUTINE
- PAZIENTI HIV POSITIVI IN TERAPIA RETROVIRALE E CON VALORI DI CD4 > 200/mm3 DEVONO RICEVERE IL TRATTAMENTO STANDARD
- LA BIOPSIA DI UNA LESIONE RESIDUA PRIMA DI TRE MESI DAL TERMINE DELLA CRT NON DEVE ESSERE PRESA IN CONSIDERAZIONE

cancers

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PROSPETTIVE FUTURE

Review

Evolution of the Role of Radiotherapy for Anal Cancer

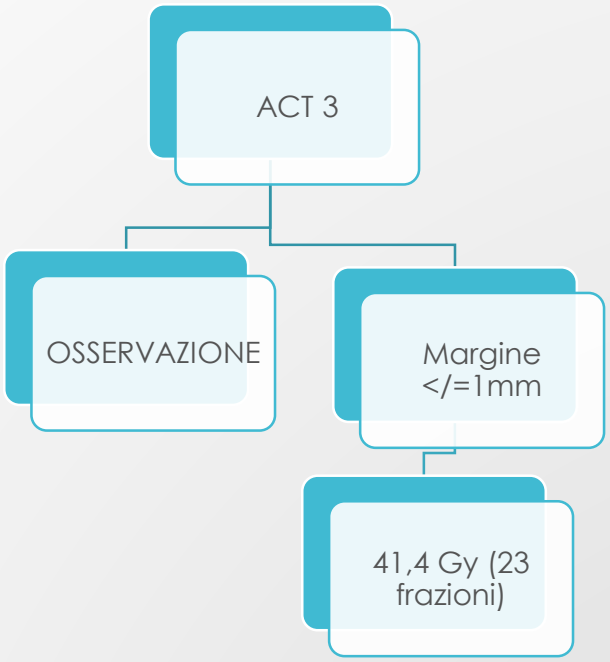
Edward Christopher Dee [1], James D. Byrne [2] and Jennifer Y. Wo [1,3,*]

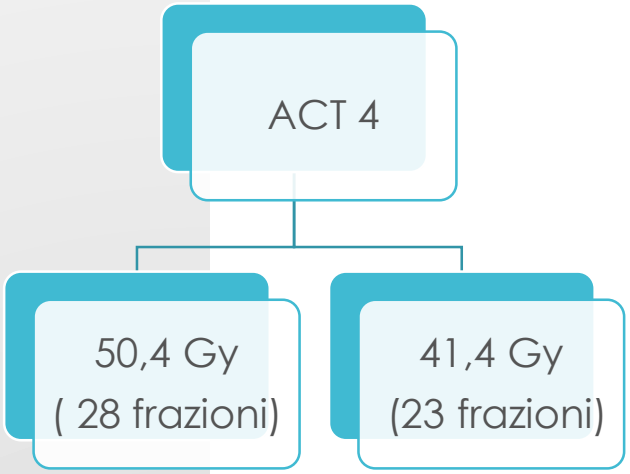
Trial/NCT ID	Inclusion	Design	Treatments
RT dose escalation vs. de-escalation			
ECOG-DECREASE [75]	T1-2N0M0	Randomized phase II: standard-dose CRT vs. de-intensified CRT	28 fractions vs. de-intensified 20–23 fractions of IMRT with MMC and 5FU or capecitabine Standard: T1-T2 N0: 50.4 Gy to primary tumor with 42 Gy to elective nodal regions, all in 28 fractions De-intensified: T1 N0: 36 Gy to primary tumor with 32 Gy to elective nodal regions, all in 20 fractions T2 N0: 41.4 Gy to primary tumor with 34.5 Gy to elective nodal regions, all in 23 fractions
ACT III [76,157]	T1N0	Single-arm phase II: dose reduced CRT	No RT for >1 mm margin; for <1 mm margin, 41.4 Gy in 23 fractions
ACT IV [76,157]	T1-2, N0	Randomized phase II: standard chemotherapy (5FU/MMC) and standard vs. de-intensified RT	Standard RT arm of 50.4 Gy in 28 fractions or de-intensified radiation arm of 41.4 Gy in 23 fractions
ACT V [76,157]	T3-4, N0-X	Randomized phase II/III: Standard chemotherapy (5FU/MMC) with standard vs. 2 escalated radiation doses	53.2 Gy, 58.8 Gy, or 61.6 Gy all in 28 fractions with standard concurrent chemo. One of the dose-escalation arms will proceed to phase III

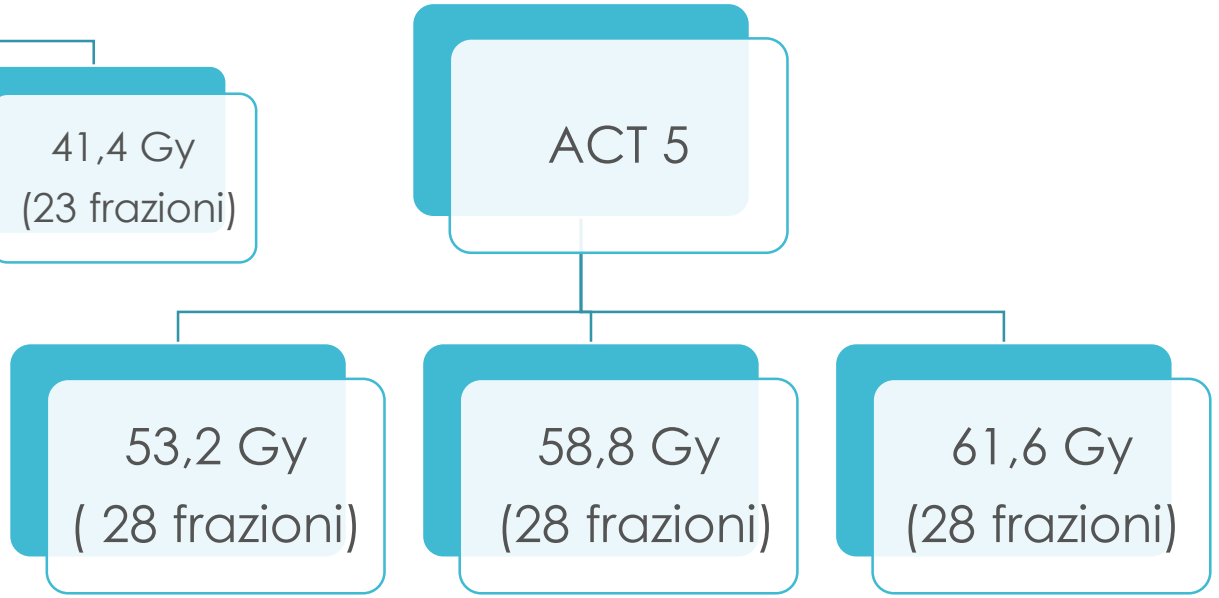
DOSE/ MODULAZIONE/ VOLUME

ON GOING PLATO TRIALS

PROSPETTIVE FUTURE







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cancers

Review

Evolution of the Role of Radiotherapy for Anal Cancer

Edward Christophe

Proton therapy			
NCT03690921 (MDACC)	Non-metastatic disease	Single-arm phase II trial assessing adverse effects of proton RT and standard chemotherapy (cisplatin and 5FU)	Linear energy transfer (LET)-optimized intensity-modulated proton therapy (IMPT)
NCT03018418 (Cincinnati)	T2-4 disease with any N	Prospective pilot study evaluating the feasibility of intensity-modulated proton therapy in reducing RT toxicity	Primary target volume 50.4–54 CGE in 28–30 fractions; nodal volumes 42–54 CGE in 28–30 fractions, with 5FU and MMC
NCT04462042 (Umeå University /Sweden)	T2 (>4 cm)-4, N0-1c, M0	Open label, multi-center, randomised phase II study, comparing proton to photon RT	Photon: primary tumor and nodal metastases >2 cm 57.5 Gy in 27 fractions (VMAT/IMRT/tomotherapy); nodal metastases up to 2 cm will receive 50.5 Gy in 27 fractions; elective nodes will receive 41.6 Gy Proton: spot scanning, total dose to the primary tumor target and node metastases >2 cm is 57.5 Gy(RBE) in 27 fractions; nodal metastases up to 2 cm will receive 50.5 Gy(RBE) in 27 fractions; elective nodes will receive 41.6 Gy(RBE)

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Review

Evolution of the Role of Radiotherapy for Anal Cancer

Edward Christopher I

Immuno-oncology			
NCT03233711	stage IIB (T3N0M0 only), IIIA (T2N1M0), IIIB (T4N0M0), or IIIC (T3N1M0, T4N1M0) invasive squamous cell carcinoma of the anus or anorectum	Randomized phase III trial of nivolumab after combined modality therapy	Up to 6 months of nivolumab IV vs. up to 6 months of observation
NCT02919969	Metastatic anal cancer with no limitations to prior treatment	Phase II study of pembrolizumab	Pembrolizumab 200 mg IV infusion every 3 weeks
NCT03519295	Unresectable locally advanced, recurrent, or metastatic squamous cell anal carcinoma	mDCF (docetaxel, cisplatin, 5FU) with vs. without atezolizumab	8 cycles of mDCF with vs. without MPDL3280A (atezolizumab) for 12 months
NCT04230759 (RADIANCE trial)	Locally advanced disease (IIB: T3N0M0; IIIA: T1-2N1M0; IIIB: T4N0M0; IIIC: T3-4N1M0; T2 > 4 cm Nany)	Phase II trial assessing the efficacy of durvalumab in combination with CRT with MMC + 5FU	53.2–58.9 Gy with nodal and elective nodal irradiation, with MMC + 5FU, with vs. without 12 doses of durvalumab
		of systemic therapy	
NCT04444921	Inoperable, recurrent, or metastatic disease	Randomized phase III trial of nivolumab with chemotherapy in treatment-naive metastatic anal cancer	Carboplatin and paclitaxel with vs. without nivolumab
NCT01285778	T2-4, any N	Phase II assessing the efficacy and toxicity of radiotherapy with 5FU, MMC, and panitumumab	Radiation therapy will be administered concurrent with chemotherapy and panitumumab treatment (IV over 8 weeks)
		Phase III double-blind	

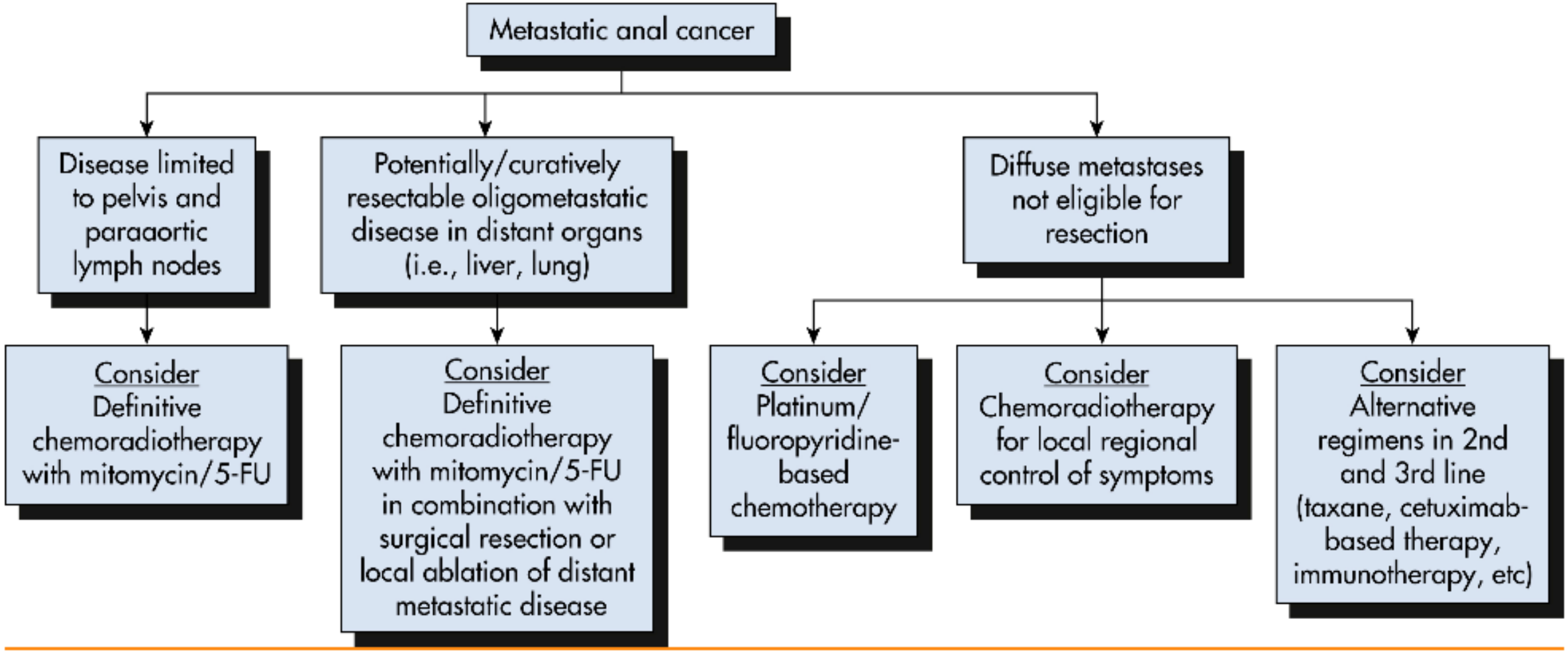

FIG. 4

Treatment algorithm: Metastatic anal cancer. 5-FU, 5-Fluorouracil.

From Niederhuber JE: *Abeloff's Clinical Oncology* ed 6, Philadelphia, 2020, Elsevier.