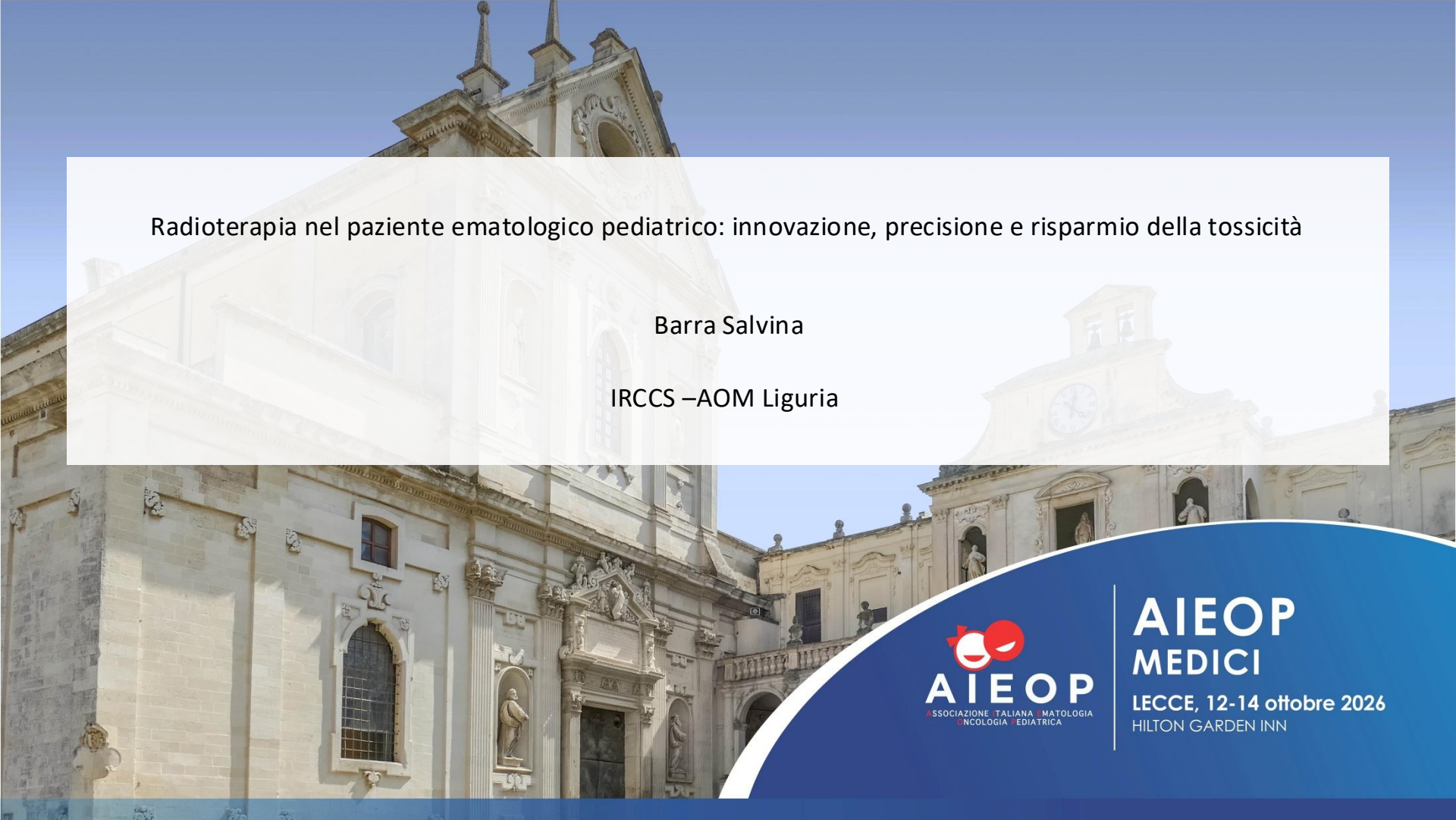


Radioterapia nel paziente ematologico pediatrico: innovazione, precisione e risparmio della tossicità

Barra Salvina

IRCCS –AOM Liguria

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

AIEOP MEDICI
LECCE, 12-14 ottobre 2026
HILTON GARDEN INN



PENTEC
Pediatric Normal Tissue Effects in Clinic
Defining Pediatric Cancer Therapy Dose-Tolerances: an International Consortium

Int J Radiation Oncol Biol Phys, Vol. 119, No. 2, pp. 313–314, 2024

PROTOCOLLI CLINICI IN CUI E' INCLUSA LA RADIOTERAPIA

1. Neuroblastoma HR-NBL2/SIOPEN
2. Rabdomiosarcoma EpSS RMS 2005 non metastatico
3. Medulloblastoma PENT 5, HR
4. Ependimoma SIOP EPD II
5. Tumore intrinseco del tronco DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)
6. Gliomi alto grado
7. Linfoma di HD Euro-Net-PHL-C2
8. Tumore di Willis UMBRELLA PROTOCOL SIOP-RTSG 2016
9. Tumore di Ewing
10. TMO

80% of these patients will survive ≥ 5 years. One study from the Childhood Cancer Survivor Study included a cohort of 25.000 patients at 5-year survivors of childhood cancer diagnosed from 1970 to 1999 from 31institutions in North America. With a median follow-up of 21 years (range, 5-38 years), **3958 deaths occurred during the 1970 to 1999 study period, with 51% attributable to recurrence or progression of the primary cancer, 41% to health-related causes other than the primary cancer, and 8% to external causes. Of the 1618 deaths related to other health-related causes, 46% were due to subsequent malignant neoplasms, 15% cardiac, and 13% pulmonary causes**

Seminars in Radiation Oncology

Translating Between Radiation Dose and Late Toxicity for Lymphoma Survivors: Implications on Toxicity Counseling and Survivorship

Semin Radiat Oncol 35:27–39 © 2024

Outcome	Cohort	Reference group	Relevant Findings, including: - Relative Risks, RR, (95% CI) - Dose Relationships, ERR or EOR/Gy (95% CI) - Standardized Incidence Ratio, SIR (95% CI) - Hazard Ratio, HR (95% CI)
Any cardiac event	The Netherlands (hospital-based) N = 2,524 (1,713 events) Median 27 yo Treated 1965-1995	No mediastinal RT	- Radiotherapy alone: SIR 3.4 (1.9-5.5) - Radio/chemotherapy: SIR 3.4 (2.2-5.1) >0-29 Gy¶: HR 2.3 (1.3-3.8) 30-35 Gy¶: HR 3.1 (2.3-4.2) ≥36 Gy¶: HR 3.8 (3.0-5.0) Patients treated with mediastinal RT had a 40 year cumulative incidence of 54.6% (51.2-57.9)
All Solid Cancers	Netherlands (hospital-based) N = 3,905 (Hodgkin lymphoma) Median 29 yo	General population	SIR = 4.2 (3.9-4.5)

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Translating Between Radiation Dose and Late Toxicity for Lymphoma Survivors: Implications on Toxicity Counseling and Survivorship

Semin Radiat Oncol 35:27–39 © 2024

Outcome	Cohort	Reference group	Relevant Findings, including: - Relative Risks, RR, (95% CI) - Dose Relationships, ERR or EOR/Gy (95% CI) - Standardized Incidence Ratio, SIR (95% CI) - Hazard Ratio, HR (95% CI)
Second Cancers			
Breast cancer	International population-based N = 3,817 (105 cases and 266 controls) Median 22 yo (all ≤30)	0-3.9 Gy*	≥4 Gy*: RR 3.2 (1.4-8.2) ERR/Gy = 0.15 (0.04-0.73)†
Lung cancer	International population-based N = 19,046 (227 cases and 455 controls) Median 50 yo (9-81) Treated 1965-1994	<5 Gy*	≥5 Gy*: RR 5.9 (2.7-13.5) ERR/Gy = 0.15 (0.06-0.39)†
Esophageal cancer	International population registry N = 19,882 (36 cases and 71 controls) Median 34 yo Treated 1943-1992	<30 Gy*	≥30 Gy*: RR 4.3 (1.5-15.3) ERR/Gy = 0.38 (0.04-8.17)†
Stomach cancer	International population registry N = 19,882 (89 cases and 91 controls)	<25 Gy*	≥25 Gy*: RR 5.8 (3.0-12.3) ERR/Gy 0.09 (0.04-0.21)†

ELSEVIER
Seminars in Radiation Oncology

Translating Between Radiation Dose and Late Toxicity for Lymphoma Survivors: Implications on Toxicity Counseling and Survivorship

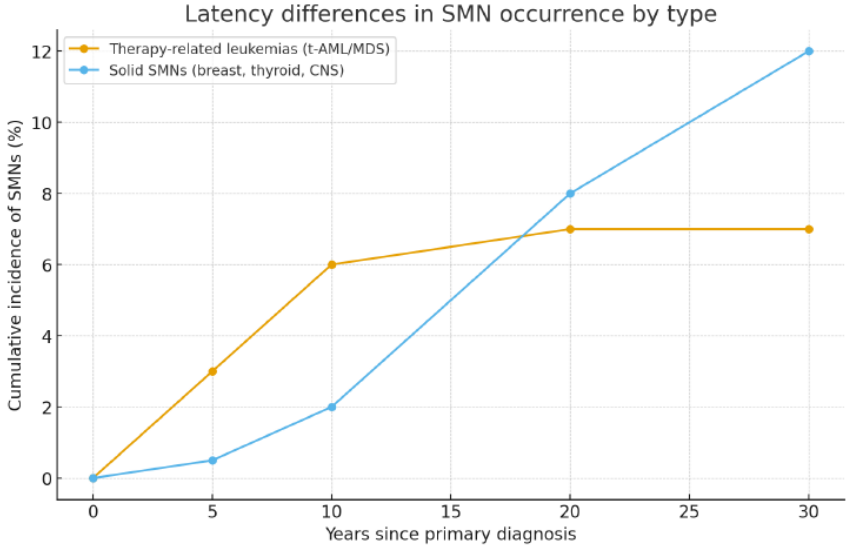
Outcome	Cohort	Reference group	Relevant Findings, including: - Relative Risks, RR, (95% CI) - Dose Relationships, ERR or EOR/Gy (95% CI) - Standardized Incidence Ratio, SIR (95% CI) - Hazard Ratio, HR (95% CI)
Cardiovascular Disease			
Coronary heart disease	The Netherlands (hospital-based) N = 2,617 (325 cases and 1204 controls) Median 32 yo (all <51) Treated 1965-1995	Case-control	20 Gy MHD* = RR 2.48 (1.66-3.96) ERR/Gy 0.074 (0.033-0.148)† For age <28 yo - ERR/Gy = 0.20 For age 28 to ≤36 yo - ERR/Gy = 0.088 For age >36 yo - ERR/Gy = 0.042
Valvular heart disease	The Netherlands (hospital-based) N = 1,852 (89 cases and 200 controls) All <41 yo Treated 1965-1995	Case-control	≤30 Gy:* RR 1.4 (0.5-3.8) 31-35 Gy*: RR 3.1 (1.7-5.6) 36-40 Gy*: RR 5.4 (3.9-7.7) >40 Gy*: RR 11.8 (4.9-28.5) $RR = 1+e^{(-5.02)} * sumVD * e^{(0.075*sumVD)}$ $P_{trend}<0.001$ (nonlinearity)
Congestive heart failure	The Netherlands (hospital-based) N = 2,617 (91 cases and 278 controls) Median 28 yo (all<51) Treated 1965-1995	Case-control	1-15 Gy:* RR 1.27 (0.86-1.89) 16-20 Gy*: RR 1.65 (0.98-2.77) 21-25 Gy*: RR 3.84 (1.97-7.47) ≥26 Gy*: RR 4.39 (2.00-9.65) $RR = 1+e^{(-4.12)} * MLVD * e^{(0.06*MLVD)} + e^{0.97} * d_{anthra}$ d_{anthra} = 1 if anthracyclines are given d_{anthra} = 0 if no anthracyclines are given
Cerebrovascular events	The Netherlands (hospital-based) N = 2,201 (96 events) Median 28 yo (all <51) Treated 1965-1995	General population	Stroke: - Radiotherapy alone: SIR 2.0 (1.2-3.1) - Radio/chemotherapy: SIR 2.6 (1.9-3.5) TIA: - Radiotherapy alone: SIR 3.4 (1.9-5.5) - Radio/chemotherapy: SIR 3.4 (2.2-5.1)

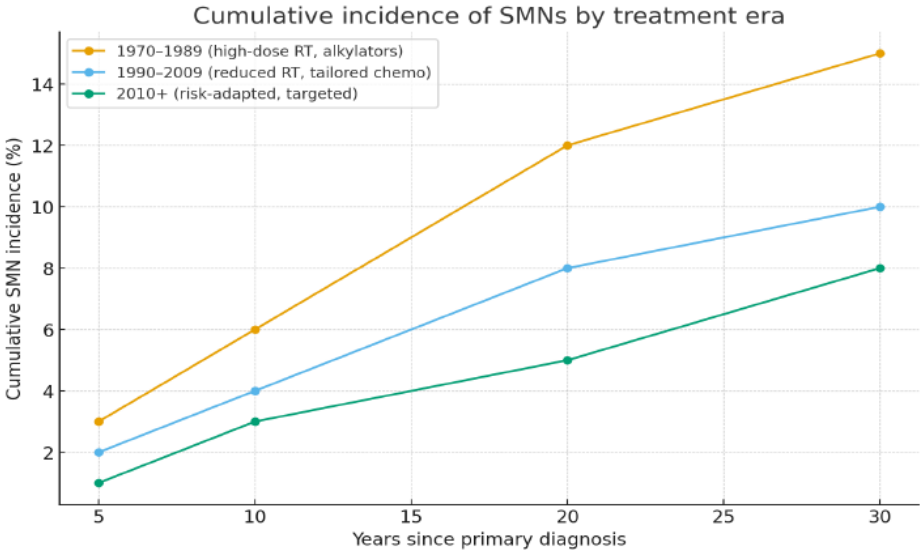
children

Systematic Review

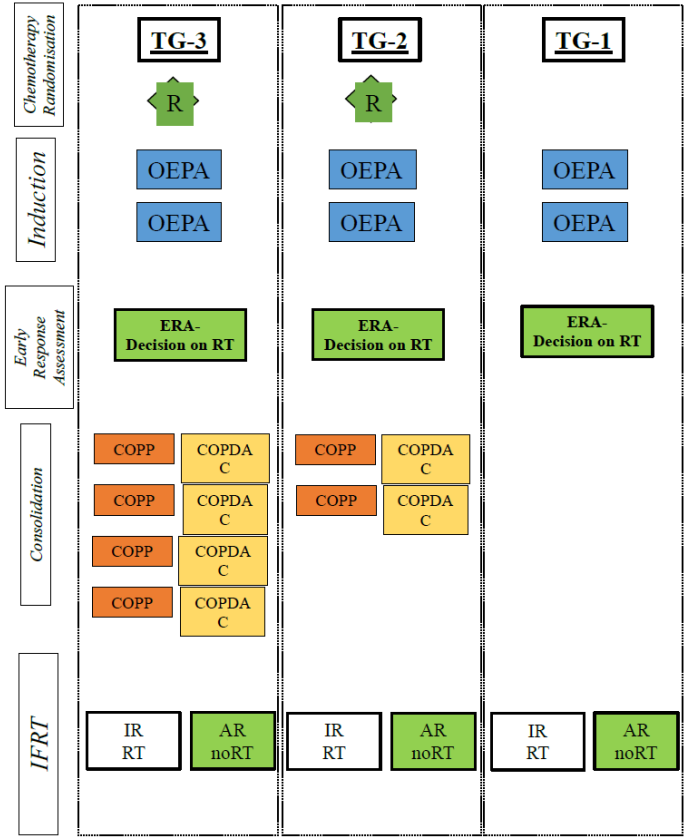
Secondary Neoplasm in Survivors of Childhood Hematological Malignancies—Systematic Review

Children **2026**, 13, 205



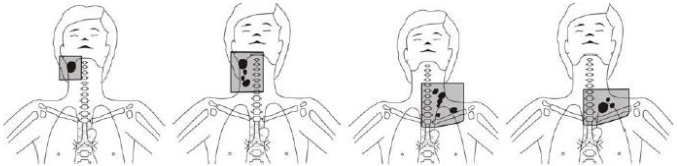


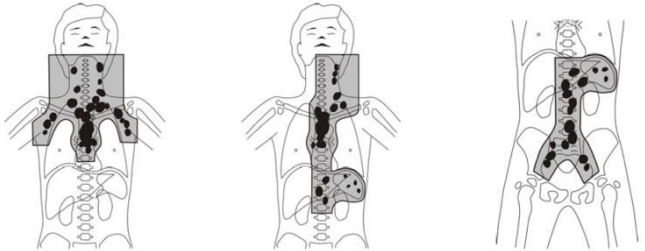
EuroNet-PHL-C1: Radiotherapy



COPDAC less gonadotoxic

EuroNet-PHL-C1: Radiotherapy





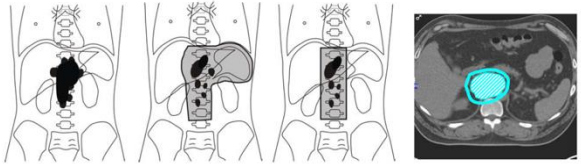


Fig. 29a | Fig. 29b Modified Involved field (PTV_1) | Fig. 29c boost (PTV_2) | Fig. 29d GTV and CTV

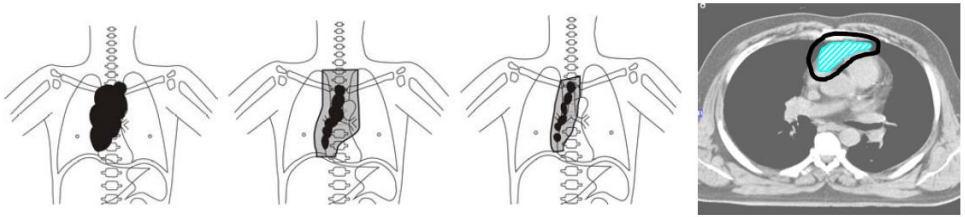


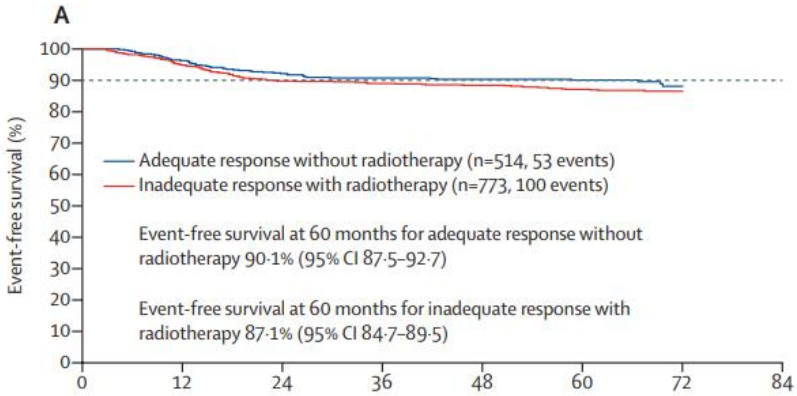
Fig. 28a | Fig. 28b Modified involved field (PTV_1) | Fig. 28c boost (PTV_2) | Fig. 28d GTV and CTV

Modified involved field radiotherapy (MIF) contains the involved lymph node(s) as recorded before chemotherapy plus a safety margin of 1-2 cm taking into account the area of involvement.(PTV1) Dose 19.80 Gy

The boost planning target volume is defined by the tumour extent, the lymph nodes, with poor response after two cycles of chemotherapy with a 1-2cm safety margin (PTV2). Dose 10 Gy

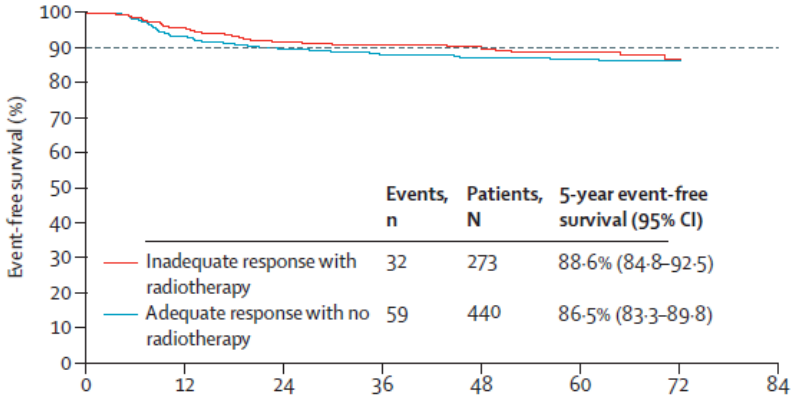
Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial

Lancet Oncol 2022; 23: 125–37

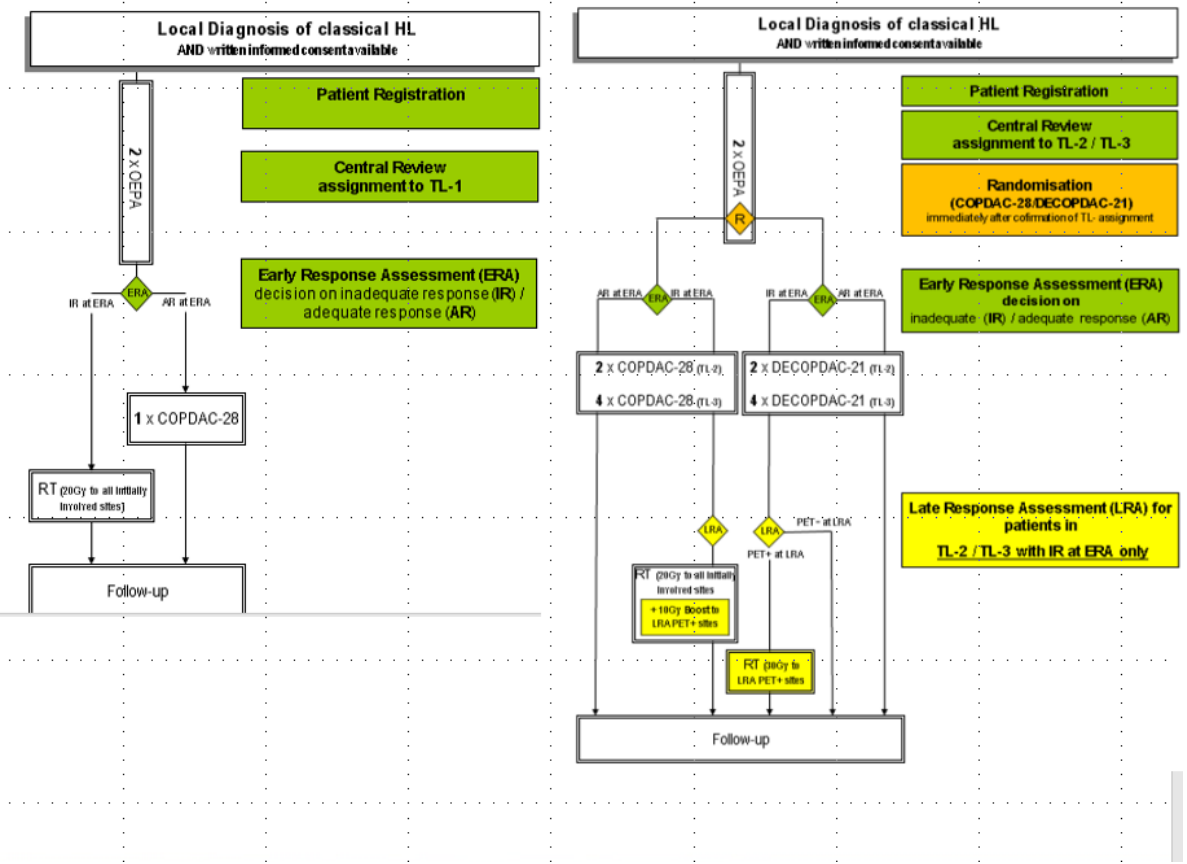


Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and an adequate response to vincristine, etoposide, prednisone, and doxorubicin (EuroNet-PHL-C1): a titration study

Lancet Oncol 2023; 24: 252–61



EuroNet-PHL-C2: Radiotherapy



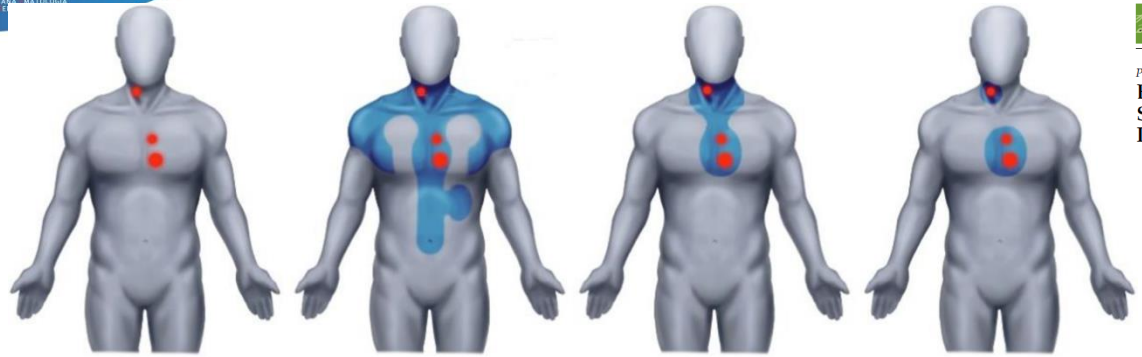
Nel protocollo tutti i pazienti che dopo II cicli di OEPA e con PET ERA negativa no RT

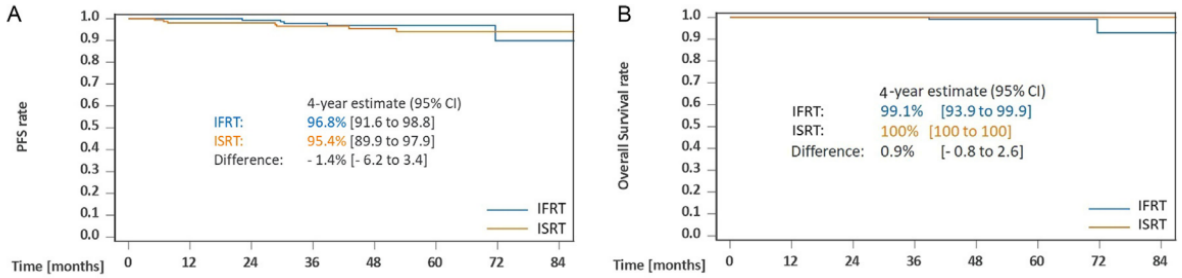
Se PET ERA positiva :

TL1 RT su tutte le sedi iniziali 19.80 Gy

TL2/3 braccio COPDAC 28 RT su tutte le sedi positivi 19.80 Gy
e se **PET LATE positiva** anche boost di 10 Gy

TL2/3 braccio DECOPDAC se **PET LATE positiva** RT solo sulle sedi positive e **se PET LATE negativa no RT**





lymphatics MDPI

Perspective

Evolution of Radiation Fields from Involved Field to Involved Site—A Summary of the Current Guidelines by the International Lymphoma Radiation Oncology Group

IFRT

Consiste nell'irradiare l'intera regione linfonodale inizialmente coinvolta dalla malattia, anche se solo una parte di essa era effettivamente affetta dal linfoma.

È stata lo standard di cura per molti anni, riducendo il campo rispetto alle tecniche precedenti (come l'extended-field RT), ma comunque coinvolgendo aree più ampie rispetto alle tecniche più moderne.

ISRT

Irradia solo il sito specifico dei linfonodi inizialmente coinvolti, tenendo conto delle variazioni anatomiche tra le immagini pre- e post-chemioterapia.

È una tecnica più mirata rispetto all'IFRT, sviluppata per ridurre ulteriormente il volume di tessuto sano esposto alle radiazioni.

La definizione di ISRT si basa sulle linee guida dell'International Lymphoma Radiation Oncology Group (ILROG) e rappresenta un'evoluzione rispetto all'INRT (Involved-Node Radiation Therapy che richiede imaging pre-chemioterapia in posizione di radioterapia,), spesso non sempre disponibile nella pratica clinica.

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

CLINICAL INVESTIGATION

Involved-site Radiation Therapy is Equally Effective and Less Toxic Than Involved-field Radiation Therapy in Patients Receiving Combined Modality Treatment for Early-stage Unfavorable Hodgkin Lymphoma—An Analysis of the Randomized Phase 3 HD17 Trial of the German Hodgkin Study Group

Int J Radiation Oncol Biol Phys, Vol. 120, No. 5, pp. 1344–1352, 2024

Preprints with THE LANCET

Response-Adapted Omission of Radiotherapy With One COPDAC Consolidation Cycle in Early-Stage, Favourable Paediatric Classical Hodgkin Lymphoma: Results From the EuroNet-PHL-C2 Trial

28 Pages • Posted: 13 Aug 2026

Maurizio Mascarin, Lars Kurch, Ana Fernández-Teijeiro et all

In early-stage cHL without risk factors, response-adapted consolidation with one COPDAC cycle achieved a 5-year EFS of 95.7% in adequate responders, significantly above the 90% target, while eliminating radiotherapy in 87% of patients. These findings support response-adapted, radiotherapy-free treatment as a standard of care in this population

Se valutiamo il periodo libero da progressione AR 95.7% (No RT) vs IR 94.4 % (Si RT) a 6 aa
RT riesce a recuperare i pazienti meno responsivi alla CT dimostrando una efficacia al pari della CT.

2. aumento della tossicità ? Si SIR II tumori 4.2
SIR danni cardiaci RT 3.4 (> 0-29 Gy HR 2.3)



INTERNATIONAL SYMPOSIUM ON HODGKIN LYMPHOMA

ABSTRACT T086

EFFICACY AND TOLERABILITY IN DECOPDAC21 VERSUS COPDAC28 IN PEDIATRIC INTERMEDIATE AND ADVANCED STAGE CLASSICAL HODGKIN LYMPHOMA: INTERIM RESULTS OF THE EURONET-PHL-C2 RANDOMIZED STUDY

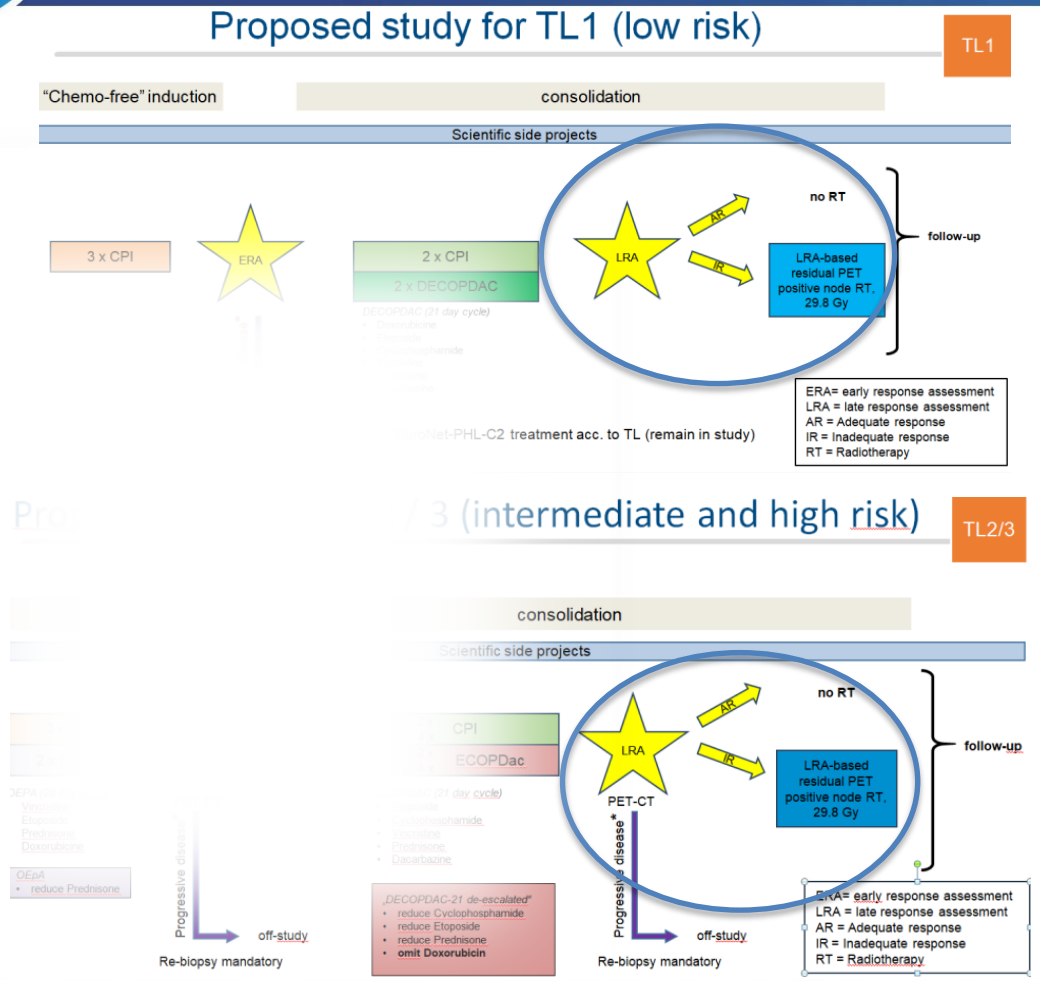
TL2 and TL3 cohort comprised 2436 pts, 2261 were randomized. Of 2249 evaluable pts, **1445 had AR** and **804 had IR after induction**.

In the ERA-AR group, **709 pts received DECOPDAC21 and had 96.0% EFS** and **710 pts received COPDAC28 with 91.2% EFS**

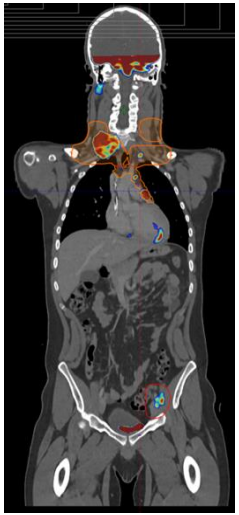
In the ERA-IR subgroup, **389 pts received DECOPDAC21 and had 85.7% EFS** and **385 pts received COPDAC28 with 88.3% EFS**

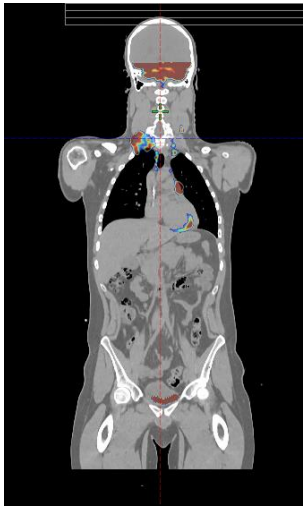
In the **DECOPDAC21 arms 12.8% received RT**, whereas, in **COPDAC28 35.6% received IFRT**.

In the ITT analysis 4/1445 AR pts (all COPDAC28) and 6/804 IR pts died, 2 in DECOPDAC21 and 4 in COPDAC28.

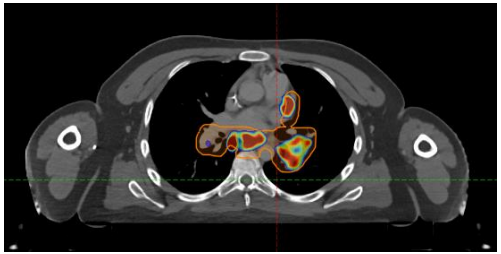


RT ISRT solo sulle sedi PET positive alla LATE PET dose 29.8 Gy









Gruppo terapeutico TL3 braccio COPDAC 28
ER-PET inadeguata
LATE-PET positiva su mediastino e ili

Confronto della dose media OAR

Braccio COPDAC 28 RT 19.8 Gy su tutte le sedi iniziali + Boost 10.Gy

Braccio DECOPDAC 21 RT 29.8 Gy

OAR(29.8 Gy)	COPDAC 28	DECOPDAC 21
Cuore	9.91	8.69
Art. cor. disc. sx	5.37	4.23
Pol dx	10.91	10.53
Pol sx	11.6	10.73
polmoni	11.25	10.63
toroide	18.39	1.42

Table 1. Normal tissue dose constraint guidelines.[a]

Organ	Recommended constraint[b]	Acceptable variation[c]
Head and neck		
Lacrimal gland	V20 Gy < 80%[5]	V20 Gy ≥ 80%[5]
Lens	D0.03 cc < 6 Gy[7]	D0.03 cc < 10 Gy[7]
Eyelid/meibomian gland	Mean < 20 Gy[8]	Mean < 24 Gy[8]
Cornea	D0.03 cc < 30 Gy[8]	D0.03 cc < 40 Gy[8]
Retina	D0.03 cc < 35 Gy[8]	D0.03 cc < 45-50 Gy[6,7,23]
Optic nerve	D0.03 cc < 50 Gy[29]	D0.03 cc < 54 Gy[23]
Optic chiasm	D0.03 cc < 50 Gy[29]	D0.03 cc < 54 Gy[23]
Brainstem	D0.03 cc < 52 Gy[7,30]	D0.03 cc < 54 Gy[7,30]
Cochlea (individual)	Mean < 35 Gy[31,32]	Mean < 45 Gy[31,32]
Hippocampus	D100% < 9 Gy[9,33]	D100% < 10 Gy[9,33]
	D0.03 cc < 16 Gy[9,33]	D0.03 cc < 17 Gy[9,33]
Pituitary gland	Mean < 30 Gy[34]	Mean < 40 Gy[34]
Spinal cord	D0.03 cc < 45 Gy[23]	D0.03 cc < 50 Gy[23]
Oral cavity	Mean < 11 Gy[11]	Mean < 30 Gy[23]
Parotid gland (ipsilateral)	Mean < 11 Gy[11]	Mean < 26 Gy[10]
Parotid gland (contralateral)	Mean < 5 Gy[12]	Mean < 12 Gy[10]
Submandibular gland (ipsilateral)	Mean < 11 Gy[11]	Mean < 39 Gy[10]
Submandibular gland (contralateral)	Mean < 5 Gy[12]	Mean < 12 Gy[10]
Larynx	Mean < 25 Gy[35]	Mean < 30 Gy[36]
Pharyngeal constrictors	Mean < 25 Gy[35]	Mean < 40 Gy[37]
Thyroid gland	V25 Gy < 63.5%[38]	V25 Gy < 70%[24]
	Mean < 28 Gy[39]	Mean < 30 Gy[40]
Thorax		
Brachial plexus	D0.03 cc < 54 Gy	D0.03 cc < 60 Gy[41]
Heart	Mean < 8 Gy[13]	Mean < 15-20 Gy[13,e]
Tricuspid valve	Mean < 5 Gy[15]	Mean < 10 Gy[15]
Aortic and mitral valves	D0.03 cc < 25 Gy	D0.03 cc < 30 Gy[42]
Pulmonic valves	D0.03 cc < 30 Gy	D0.03 cc < 35 Gy[42]
Left ventricle	Mean < 8 Gy[13]	Mean < 15 Gy[13]
Left anterior descending artery	V15 Gy < 10%[15]	V15 Gy < 15%[15]
Left circumflex artery	V15 Gy < 14%[15]	V15 Gy < 20%[15]
Right coronary artery	Mean < 5 Gy[15]	Mean < 10 Gy[15]
Lungs	Mean < 10 Gy[24]	Mean < 13.5-20 Gy[43,e]
	V20 Gy < 20%[43]	V20 Gy < 30-40%[43,e]
Esophagus	Mean < 30 Gy[23]	Mean < 34 Gy[45]
Breast	Mean < 4 Gy[46]	Mean < 10 Gy[27]
Abdomen		
Liver	Mean < 15 Gy[47]	Mean < 24-30 Gy[48,e]
Stomach	D0.03 cc < 45 Gy	D0.03 cc < 50-54 Gy[50,e]
Spleen	Mean < 10 Gy[51]	Mean < 20 Gy[52]
Pancreas	Mean < 10 Gy[53]	Mean ≤ 21 Gy[53]
Duodenum	D0.03 cc < 45 Gy	D0.03 cc < 50-55 Gy[50,e]
Small bowel (loops)	V15 Gy < 120 cc[50]	V30 Gy < 155 cc[55]
	D0.03 cc < 45 Gy	D0.03 cc < 50-54 Gy[50,e]
Large bowel	D0.03 cc < 45 Gy	D0.03 cc < 50-60 Gy[50,e]
Bowel bag	V45 Gy < 165 cc[50]	V45 Gy < 195 cc[50]
Kidney (individual)	Mean <5 Gy[56]	Mean < 8-18 Gy[57]
Kidneys (bilateral)	V5 Gy < 58%[58]	
Bone marrow	V10 Gy < 50%	V10 Gy < 80%[20]
	V25 Gy < 25%	V25 Gy < 50%[59]
Long bone	Mean < 37 Gy[60]	Mean ≥ 37 Gy[60]
	V40 Gy < 35%[61]	V40 Gy < 64%[61]
Bladder	Mean < 40 Gy[62]	Mean < 44 Gy[62]
Rectum	V60 Gy < 35%[63]	V60 Gy ≥ 35%[63]
Cauda equina, sacral plexus	D0.03 cc < 54 Gy	D0.03 cc < 60 Gy
Testes	Mean < 1 Gy[64]	Mean < 2 Gy[64]
Ovaries	Mean < 2 Gy[65]	Mean < 4 Gy[65]
	Mean < 2 Gy[65]	Mean < 10 Gy[65]

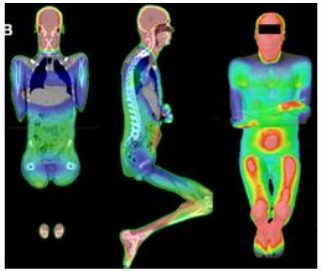
OXFORD

JNCI: Journal of the National Cancer Institute, 2026, 00(00), 1–7
https://doi.org/10.1093/jnci/djag112
Advance Access Publication Date: April 8, 2026
Commentary

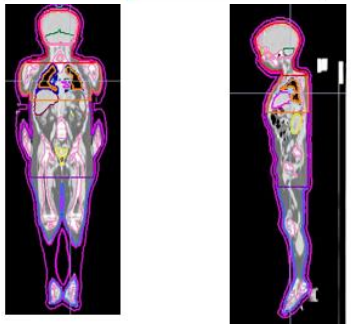
Consensus radiation therapy organ at risk constraints for NCTN trials in hematologic malignancies

Il documento pubblicato è stato redatto da tutti i radioterapisti di tutti i principali gruppi cooperativi della National Clinical Trials Network (NCTN).

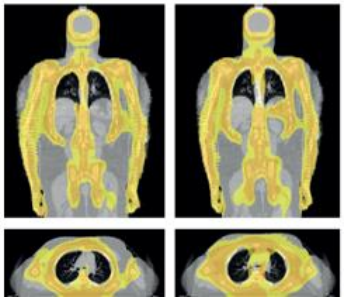
Dalla TBI 2-D



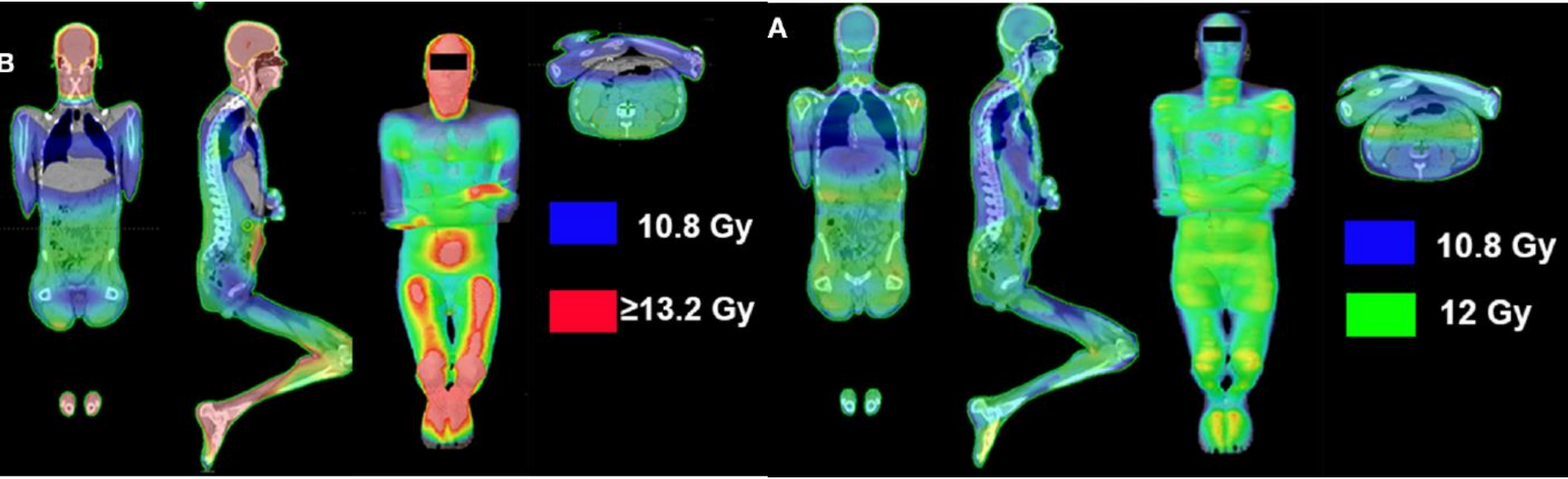
TBI in TOMO



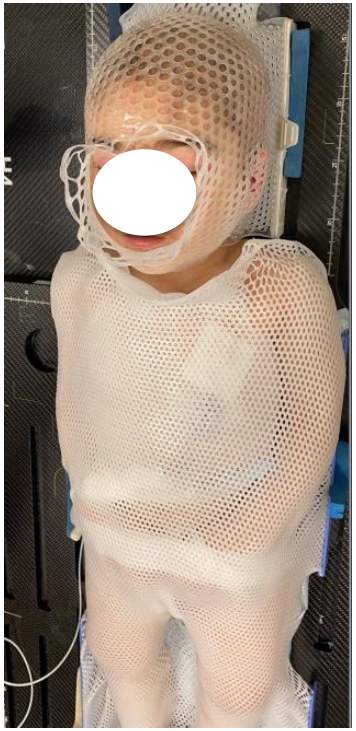
TMI TMLI



2D **VS** **IMRT(Intensity Modulated Radioterapy)**



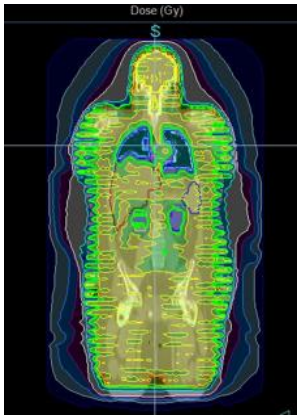
2018



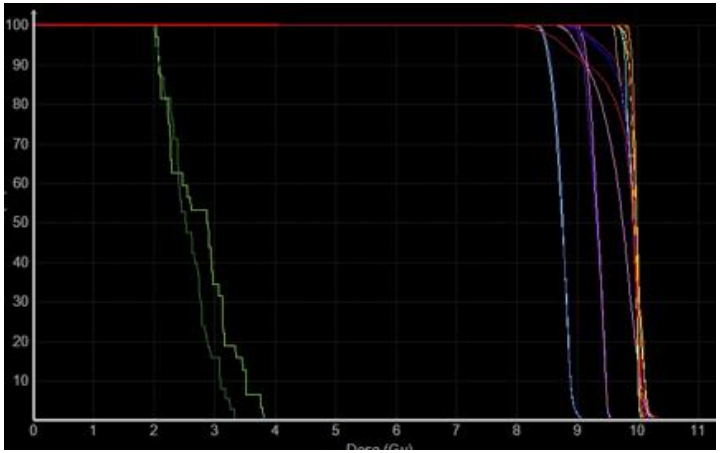
Age 23 months with Congenital Dyskeratosis receiving dose of 200 cGy TBI. Planning CT images were acquired with a slice thickness of 5 mm.

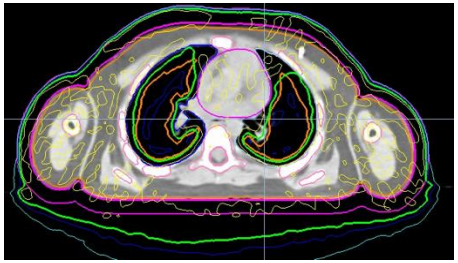
The whole-body was contoured and transferred to the HT TPS for TBI planning. To avoid calculating the dose in the skin we created an internal margin of 2 mm below the body surface. The whole body without this internal margin has been called PTV1. To reduce geometrical missing due to setup errors and patient movements a virtual bolus (VB) of 5 mm thickness was added to patient surface. The area between skin and VB has been called PTV2. VB is declared as the target of low priority for the optimization algorithm. Dose prescription to the PTV1 and PTV2 was 2 Gy in single dose.

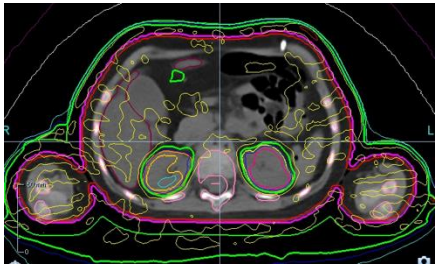
Name	max Dose [Gy]	min Dose [Gy]	Avg Dose
PTV_1	2,09	1,94	2,00
Liver	2,05	1,97	2,01
Lung R	2,04	1,98	2,01
Lung L	2,03	1,98	2,01
Brain	2,06	1,95	2,00
Body	2,10	1,09	2,00
Lens_L	2,06	2,00	2,02
Lens_R	2,04	2,00	2,02
Thyroid	2,03	1,98	2,01
Testis_L	2,02	1,98	2,00
Testis_R	2,03	2,00	2,02
Kidney_L	2,04	1,98	2,01
Kidney_R	2,03	1,98	2,00









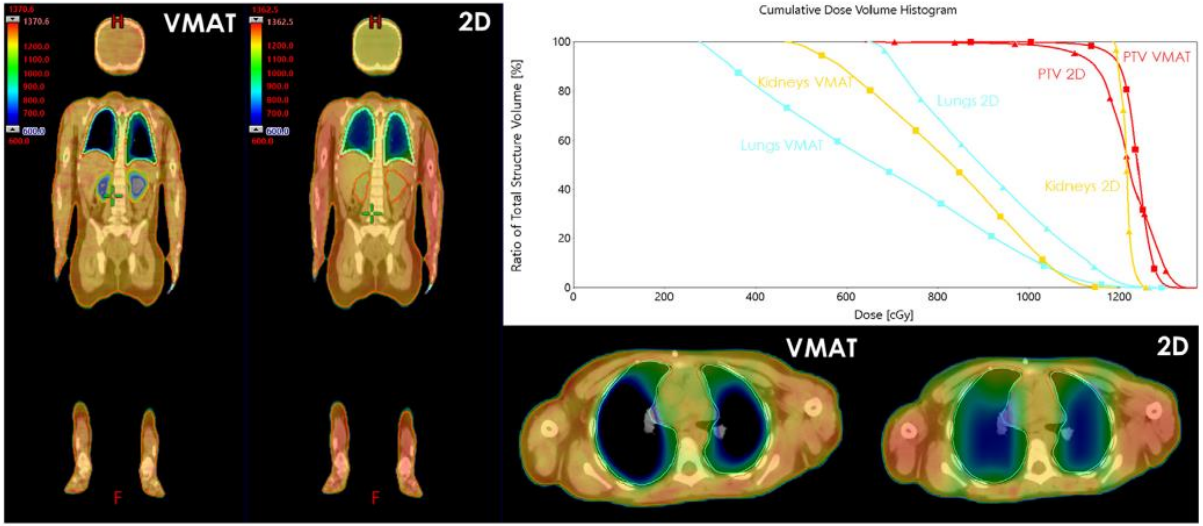


Organo	Dose media	Crop
Reni	9,9	3 mm
Cuore	9,9	5 mm
Lungs	7,9	5 mm
Tiroide	9,9	no
Ippocampi	11,7	no
Ipofisi	11,1	no
Ipotalamo	11,3	no
Cristallini	10 massimo	5 mm
PTV	12 (range 11.5-12.2)	

Esperienze di Stanford e City Hope

Received: 15 April 2024 | Revised: 21 June 2024 | Accepted: 22 June 2024
DOI: 10.1002/pbc.31185
Pediatric Blood & Cancer
SPECIAL REPORT

Incorporating intensity modulated total body irradiation into a Children's Oncology Group trial: Rationale, techniques, and safeguards



Structure	Dosimetric parameter	% of Prescription dose
PTV_Body	V100% ≥	90% goal, 85% per protocol
PTV_Body	V110% ≤	5%
PTV_Body	D98% ≥	90%
PTV_Body	D1cc ≤	120% goal, 130% per protocol
Lungs	Dmean ≤	8 Gy[a]
Lungs_Eval (Lungs-1 cm)	Dmean ≤	40%
Kidneys	D0.03cc ≤	110%
	Dmean ≤	75%
Bowel	D0.03cc ≤	110%
OralCavity	D0.03cc ≤	110%
Lenses	D0.03cc ≤	90%

I dati clinici e dosimetrici sono stati utilizzati per la TBI –IMRT nello studio COG ASCT 2031

PHO-COG-ASCT2031

A Multi-Center, Phase 3, Randomized Trial of Matched Unrelated Donor (MUD) versus HLA-Haploidentical Related (Haplo) Myeloablative Hematopoietic Cell Transplantation for Children, Adolescents, and Young Adults (AYA) with Acute Leukemia or Myelodysplastic Syndrome (MDS)

Confrontare l'incidenza cumulativa a un anno di malattia del trapianto contro l'ospite (GVHD) grave (a partire dal giorno dell'HCT) – definita come GVHD acuta (aGVHD) di grado III-IV e/o GVHD cronica (cGVHD) che richieda immunosoppressione sistemica – e confrontare la sopravvivenza libera da malattia (DFS) (dal momento della randomizzazione) in bambini e giovani adulti (AYA) affetti da leucemia mieloide acuta (AML), leucemia linfoblastica acuta (ALL), leucemia acuta a fenotipo misto (MPAL) e sindrome mielodisplastica (MDS) assegnati casualmente a haplo-HCT o a HCT da donatore adulto non familiare (MUD) compatibile 8/8. **Lo studio non sta al momento arruolando**

X. **To assess the feasibility of incorporating total body irradiation (TBI) delivered with volumetric modulated arc therapy (VMAT) or tomotherapy into a multi-institutional study, to describe the toxicities and oncologic outcomes (relapse, DFS, OS, and TRM) of the subgroup of patients treated with this approach, and to compare these outcomes to those of patients treated with conventional TBI.**

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REVIEW

Incorporating Intensity Modulated Total Body Irradiation (IMRT-TBI) Into Future Cooperative Group Clinical Trials: An NRG Hematologic Malignancies Working Group-Led Report From the National Clinical Trials Network

Int J Radiation Oncol Biol Phys, Vol. 125, No. 3, pp. 714–736, 2026

La TBI con IMRT è attualmente implementata in numerosi centri. Per consentire una valutazione coerente nei futuri studi del NCTN il gruppo ematologico del NGR ha riunito esperti di IMRT-TBI e leader dell'NCTN per elaborare raccomandazioni condivise: pianificazione, OAR, controlli di qualita', constraints . Questo per meglio valutare e omogenizzare i risultati clinici e consentirà una valutazione rigorosa degli esiti.

IMRT/TBI for Myeloblative conditioning

Structure	Dosimetric parameter	Goal, % of the prescription		Per protocol, % of the prescription	Enforcement type
PTV_Body	V100% ≥	90%		85%	**Required**
	V110% ≤	5% for pediatric, 10% for adults		10% for pediatric, 15% for adults	Recommended
	D98% ≥	90%		85%	Recommended
	D1cc ≤	120% for pediatric, 125% for adults		130%	Recommended
Lungs	D_{mean} ≤	55%	6.6 Gy	8 Gy	**Required**
Lungs_Eval (Lungs − 1 cm)	D_{mean} ≤	40%		45%	Recommended
Kidneys	D0.03cc ≤	110%		115%	Recommended
	D_{mean} ≤	70%	8.4. Gy	75%	Recommended
Bowel	D0.03cc ≤	110%		115%	Recommended
Cavity_Oral	D0.03cc ≤	110%		115%	Recommended
Lenses	D0.03cc ≤	90%	10.80 GY	95%	Recommended

Tossicità 2D vs IMRT-TBI

Tossicità	TBI 2D	TBI IMRT (VMAT/Tomo-TBI)	Riferimenti principali
Pneumonite	12-17%	0-3%	Hui et al 2024, Ladbury et al 2022, Review 2026
Nefrotossicità	34-36%	7-13%	Hui et al 2024, Zhang-Velten et al 2022, Review 2026
Mucosite orale G3+	68%	34-71%	Hui et al 2024, Keit et al 2023, Review 2026
Dermatite	35%	16%	Hui et al 2024, Review 2026
Nausea	81%	58-68%	Hui et al 2024, Review 2026
GVHD acuta	62%	42%	Hui et al 2024, Ladbury et al 2022, Review 2026
Cataratta	>50% a 10 anni (paz. pediatrici)	<5% (stimato, follow-up breve)	Bernard et al 2014, Review 2026
Recidive extramidollari	Presente	Non aumentate	Kim et al 2014, Review 2026
Fallimenti di attecchimento	Rari	Nessun aumento	Review 2026

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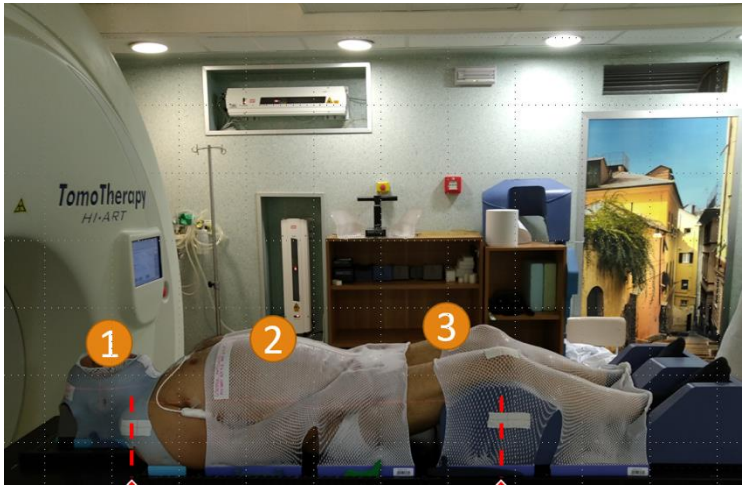
Int J Radiation Oncol Biol Phys, Vol. 125, No. 3, pp. 714–736, 2026

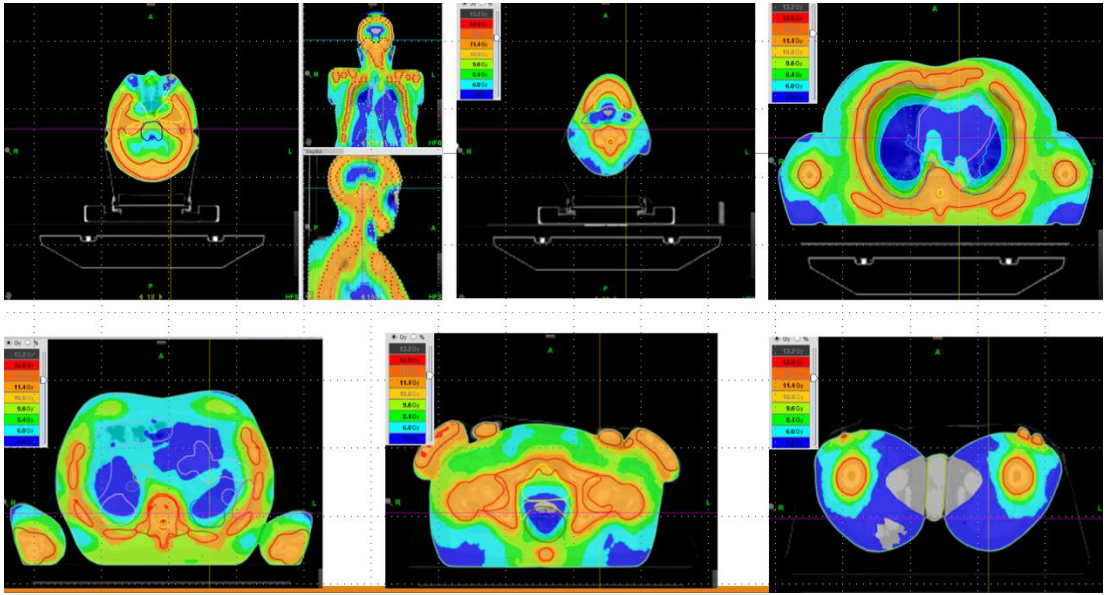
ELSEVIER
Seminars in Radiation Oncology

Radiation as an Immune Modulator: Where We Are With Modern Total Body Irradiation

Semin Radiat Oncol 35:67–86 2024

Dal 2009 TMI/TLI 132 pz





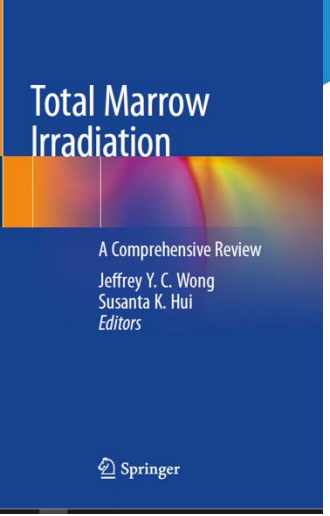


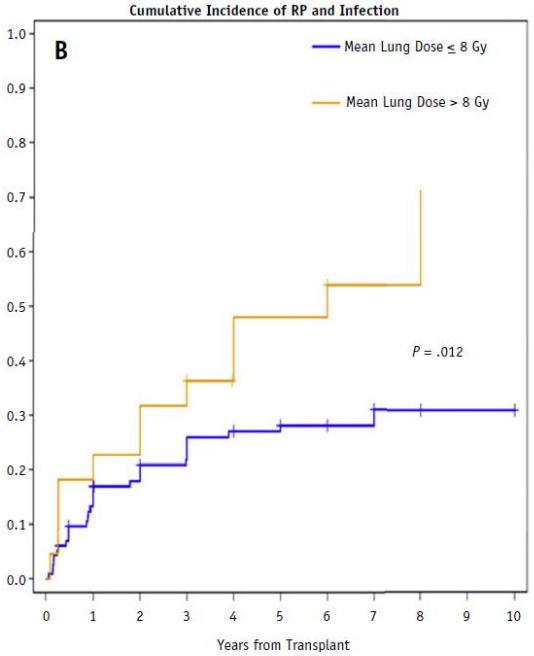
Table 6.1 Dosimetric parameters of the target coverage in TMI delivered by helical Tomotherapy and the percentage of median dose reduction to the organs at risk with TMI instead of classical TBI

Organ	Median dose reduction (%)	Range (%)
Brain	48.1	41.0–60.0
Parotid gland	29.3	15.0–43.5
Eye	52.0	30.2–60.4
Oral mucosa	42.1	20.5–50.0
Larynx	54.5	43.0–61.7
Thyroid	48.4	27.5–51.0
Lung	48.8	41.0–53.0
Breast	61.0	45.1–68.2
Heart	46.7	43.0–52.5
Liver	52.3	43.5–60.0
Bowel	53.7	47.7–59.5
Kidneys	63.0	47.0–73.0
Bladder	62.1	50.2–69.3
Rectum	58.4	48.2–65.2
Uterus	64.7	58.0–76.2
	PTV	
Value	**Mean (%)**	**Range (%)**
D95	93.3	91.9–94.2
D90	95.7	94.1–96.7
D5	102.9	101.7–103.8

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Clinical Investigation

Radiation-Related Toxicities Using Organ Sparing Total Marrow Irradiation Transplant Conditioning Regimens



142 patients
Median follow-up (range) for all patients was 2 years
Mean organ doses in Gy were lung 7.0, kidneys 7.1, thyroid 6.7,lens 2.8.

The crude incidence of radiation pneumonitis (RP) was 1 of 142 (0.7%). cumulative incidence of infection and RP (I/RP) was 22.7% at 2 years post-TMI.

Mean lung dose 8 Gy predicted for significantly lower rates of I/RP (2-year cumulative incidence 20.8% vs 31.8%, P <012).
No radiation-induced renal toxicity was noted. Hypothyroidism occurred in 6.0% and cataract formation in 7.0% of patients.

Tossicità	TBI IMRT (VMAT/Tomo-TBI)	TMI/TMLI	Riferimenti principali
Pneumonite	0-3%	<3%	Hui et al 2024, Ladbury et al 2022 , Kovalchuk et al 2026
Nefrotossicità	7-13%	<10%	Hui et al 2024 , Zhang-Velten et al 2022 , Kovalchuk et al 2026
Mucosite orale G3+	34-71%	0-34%	Hui et al 2024 , Keit et al 2023 , Ogawa et al 2023
Dermatite	16%	<10%	Hui et al 2024 , Kovalchuk et al 2026
Nausea	58-68%	<50%	Hui et al 2024 Kovalchuk et al 2026
GVHD acuta	42%	20-40%	Hui et al 2024 , Ladbury et al 2022 , Al Malki et al 2022
Cataratta	<5% (follow-up breve)	<5% (stimato, follow-up breve)	Bernard et al 2014 , Kovalchuk et al 2026
Recidive extramidollari	Non aumentate	Non aumentate	Kim et al 2014 , Kovalchuk et al 2026
Fallimenti di attecchimento	Nessun aumento	Nessun aumento	Kovalchuk et al 2026

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REVIEW

Incorporating Intensity Modulated Total Body Irradiation (IMRT-TBI) Into Future Cooperative Group Clinical Trials: An NRG Hematologic Malignancies Working Group-Led Report From the National Clinical Trials Network

Int J Radiation Oncol Biol Phys, Vol. 125, No. 3, pp. 714–736, 2026

TMLI Trial	PI / Country Study start - completion	Phase	Last update Clinicaltrials.gov	Population summary	Number of patients	TMLI intervention + other conditioning Primary endpoint
				Younger patients (<60 years) with relapsed/refractory (R/R) or high risk AML and ALL		
NCT04262843	City of Hope Medical Center / USA	Phase II	2024-03	Patients with ALL CR1 poor risk or CR2-3, AML intermediate/poor risk CR1 or CR2-3, or MDS high (intermediate) risk (12-60 years), before haploidentical allogeneic SCT	70	TMLI BID in 4 days, in combination with fludarabine, and high dose post-transplant cyclophosphamide Incidence adverse events by CTCAE v5 1-year GvHD-free survival (GRFS) rate, as assessed in each arm (Arm A: patients with AML or MDS and Arm B: Patients with ALL.
NCT06195891	City of Hope Medical Center / USA 2024 - 2027	Phase I	2024-11	Patients with high risk acute leukemias or MDS (60-75 years), before allogeneic SCT with partially engineered T-regulatory cell donor graft TRGFT-201 (Orca-T) from a matched or haploidentical donor.	33	TMLI BID in 4 days (dose escalation) Describe toxicities attributable to TMLI by dose level. Determine the recommended phase II dose (RP2D) of TMLI with an Orca-T for allogeneic SCT.
NCT03494569	City of Hope Medical Center / USA 2018 – 2028	Phase I	2024-02	Patients with AML, ALL, MDS (very) high risk for multiple reasons / active disease / comorbidities precluding TBI (12-55 years), before allogeneic SCT	36	TMLI (dose not given) BID in 4 days, with fixed doses of fludarabine and melphalan (FM100) To determine the MTD/RP2D of TMLI who are not eligible for standard myeloablative regimens, with either a matched donor (Arm A) or a haploidentical donor (Arm B).
						To describe toxicities attributable to TMLI by dose level in patients treated under this regimen.
NCT02094794	City of Hope Medical Center / USA 2014 - 2025	Phase II	2024-03	Patients with AML or ALL not in first remission or R/R (16-60 years, before allogeneic SCT	87	TMLI (dose not given) BID in 5 days Following a patient safety lead-in, evaluate the anti-tumor activity of the allogeneic hematopoietic cell transplant preparative regimen - TMLI, cyclophosphamide (Cy) and etoposide (VP-16), as assessed by 2-year PFS. Incidence toxicity.
NCT04976205	Italy 2021 - 2024	Single arm cohort	2022-09	Adult patients (> 18 years) with hematologic disease undergoing TMLI prior to allogeneic SCT	60	Using MRI for lymph node delineation Reduction of lymph node target volume through use of whole body-MRI.
NCT06209190	Hospital Universitario Dr. Jose E. Gonzalez, Mexico 2023 - 2024	Single arm cohort	2024-01	Patients with ALL in first remission or R/R (16-45 years), with identical or haploidentical donor, before allogeneic SCT	14	TMLI to 12 Gy in 6 fractions (2 Gy BID x 3 days), along with fludarabine and cyclophosphamide Early mortality rate (30 days, expected < 15%) Grade 3+ toxicity by CTCAE v5.
NCT06598969	Hospital Universitario Virgen del Rocio / Spain 2024 - 2028	Phase II	2024-09	Patients with high-risk MDS/AML (18-50 years), before allogeneic SCT	58	TMLI (dose not specified) plus cyclophosphamide and etoposide PFS at 2 years after safety lead-in phase
NCT02446964	City of Hope Medical Center / USA	Phase I	2024-09	Patients with high-risk ALL/AML or intermediate/high-risk MDS (12-60 years), before haploidentical allogeneic SCT	24	TMLI (dose escalation not specified) BID in 4 or 5 days, in combination with fludarabine (fludarabine phosphate) and pre-post-transplant cyclophosphamide.
						To establish safety and determine the MTD of TMLI and chemoregimen. To evaluate the safety of the regimen at each dose level by assessing adverse events. To evaluate the safety of the regimen at each dose level by assessing complications: including acute/chronic GvHD, infection and delayed engraftment.
NCT06564545, NCT06559345	First Affiliated Hospital of Zhengzhou University / China 2024 - 2029	RCT	2024-08	Patients with ALL in CR (age 1-17 or 18-65 years), before haploidentical allogeneic SCT	276	TMLI to 12 Gy in 6 fractions (2 Gy BID x 3 days) vs TBI to 12 Gy in 6 fractions (2 Gy BID x 3 days), both with cyclophosphamide Relapse-free survival (at 2 years) aGVHD within 100 days after SCT Overall survival (at 2 years)
NCT06564493, NCT06557161	First Affiliated Hospital of Zhengzhou University / China 2024 - 2029	RCT	2024-08	Patients with ALL in CR (age 1-17 years or 18-65 years), before matched sibling allogeneic SCT	170	TMLI to 12 Gy in 6 fractions (2 Gy BID x 3 days) vs TBI to 12 Gy in 6 fractions (2 Gy BID x 3 days), both with cyclophosphamide Relapse-free survival (at 2 years) aGVHD within 100 days after SCT Overall survival (at 2 years)
				Older patients (>60 years) with relapsed/refractory (R/R) AML and ALL		
NCT03467386	City of Hope Medical Center / USA 2018 - 2024	Phase I	2024-02	Patients with AML in first or second CR (16-60 years), before allogeneic SCT	18	TMLI BID in 5 days, with a post-transplant high dose cyclophosphamide (PTCy)-based GvHD prophylaxis strategy Safety/feasibility through the assessment of adverse events, also including acute GvHD,
						infection and delayed neutrophil/platelet engraftment.
NCT05139004	City of Hope Medical Center / USA 2022 - 2024	Phase I	2024-01	Patients >60 years with AML, ALL, MDS prior to allogeneic SCT. Patients 18-59 years also eligible if they are not candidates for myeloablative transplant.	12	TMLI to 12 Gy in 4 days plus fludarabine, melphalan, and escalating dose of basiliximab Maximum tolerated dose/recommended phase II dose of 90Y-DOTA-antiradioimmunotherapy (30 days post-transplant) Toxicity (30 days post-transplant)
NCT06602323	Hospital Universitario Virgen del Rocio / Spain 2024 - 2028	Phase II	2024-09	Patients ≥50 years with high risk AML/MDS who cannot undergo fully myeloablative regimen	34	TMLI to 12 Gy / 11 Gy / 10 Gy in 8 fractions BID in 4 days (liver, brain limited to 7.2 Gy). De-escalate by 1 Gy if ≥2/6 patients have DLT. In combination with fludarabine/melphalan. PFS at 2 years
NCT06287944	City of Hope Medical Center / USA 2024 - 2027	Phase I	2024-08	Patients >60 years with AML, ALL, MDS prior to allogeneic SCT, KPS > 70. Patients 18-59 also eligible if they are not candidates for myeloablative transplant.	15	TMLI 12 Gy in 4 days (BID 1.5 Gy), plus fludarabine and melphalan (FM100) with actinium Ac 225-DOTA-daratumumab (dose-escalation) CTCAE v.5.0 toxicity up to 2 years post-SCT DLT up to 30 days post-SCT MTD/RP2D – highest dose where 6 patients have been treated and 1 or less develops a DLT
				Younger patients (<60 years) with Sickle Cell disease		

NCT05384756	City of Hope Medical Center / USA 2022 - 2026	Phase I	2024-06	Patients with sickle cell disease (2-40 years), before non-myeloablative allogeneic SCT	20	TMLI to 6 Gy in 2 fractions (3 Gy BID in 1 day), with alemtuzumab, sirolimus Incidence adverse events by day 100 by CTCAE v5 Feasibility; engraftment sufficient to reduce sickle cell disease burden, at 2 years
TMI Trial	**PI / Country** **Study start - completion**	**Phase**	**Last update clinicaltrials.gov**	**Population summary**	**Number of patients**	**TMI intervention + other conditioning** **Primary endpoint**
NCT00800059	Ottawa Hospital, Ontario, Canada 2008 - 2025	I - II	2015-07	Adult R/R Multiple Myeloma patients (18-60 years), before autologous SCT	27	Gradually dose-escalated TMI (14 Gy – 28 Gy). Determination of maximum tolerated dose TMI before autologous SCT. Secondary: frequency+timing TMI; Early – Intermediate – Late MM TMI
NCT03696537	Indiana University, Indiana / USA **Terminated (extreme toxicity)** 2018 - 2021	I - II		Adult AML, ALL, MDS, CML patients (18-65 years) not in CR, with R/R disease	6	DLT of TMI in 10 fractions BID in combination with 150 mg/m2 fludarabine- Phase I MTD of TMI in 10 fractions BID in combination with 150 mg/m2 fludarabine- Phase I Overall survival (OS) rate 1 year post transplant-Phase II only [Time Frame: 1 year]
NCT06461091	Institute of Hematology & Blood Diseases Hospital, China Not yet recruiting	Cohort	2024-07	Adult (≥ 16 years) ALL patients before allogeneic SCT	20	EFS at 1 year after allogeic SCT
NCT05970198	Zhongnan Hospital of Wuhan University, China 2023 - 2027	RCT	2023-08	Adult Multiple Myeloma patients (18-75 years), before autologous SCT. ECOG < 2	58	TomoTherapy TMI to 8 Gy in 2 fractions BID CR rate 100 days after transplant *# randomization melphalan versus TMI, unclear description of TMI setup (TomoTherapy or 2D parallel opposed beams)*
NCT01665014	Marie Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland 2012 - 2016	Single cohort	2012-08	Adult Multiple Myeloma patients (18-65 years), before autologous SCT, ECOG ≤ 1	50	Double autologous SCT; TMI prior to first SCT, high-dose melphalan prior to second SCT TMI to 12 Gy (2 Gy BID x 3 days) PFS at 3 years Publication: doi: 10.1038/s41409-020-01181-x
NCT01163357	City of Hope Medical Center / USA 2011 - 2024	Phase I	2024-05	Adult Multiple Myeloma patients, TMI-containing arm for ages 18-60 years, before autologous SCT	18	TMI to 9 Gy (1.5 Gy BID x 3 days), with fludarabine, melphalan, and bortezomib (dose escalation) Determine feasibility od dose escalation and describe toxicities, MTD, DLT Publication phase I: doi: 10.1097/COC.0000000000001095
NCT03121014	University of Illinois, Chicago/USA 2017 - 2026	Phase II	2024-07	Adult high-risk AML or MDS patients (18-65 years), before allogeneic SCT	46	TMI to 9 Gy (1.5 Gy BID x 3 days) with fludarabine and busulfan Relapse-free survival, goal of 30% relapse-free survival at 1 year
NCT04187105	University of Illinois, Chicago/USA	Phase II	2024-09	Adult leukemia/MDS patients (18-75 years), before allogeneic SCT	27	TMI to 6 Gy (1.5 Gy x 2 days) with cyclophosphamide and fludarabine Relapse-free survival at 1 year
						GVHD-free survival at 1 year
NCT03262220	University Hospital, Geneva, Switzerland 2017 - 2025	Single cohort	2020-05	Adult patients with hematologic malignancy unfit for TBI (40-80 years), before allogeneic SCT	10	TMI to 12 Gy in 3 fractions with SIB of 4.5 Gy in 3 fractions to active bone marrow Grade II-III toxicity 30 days after transplant (Seattle regimen-related toxicity grade)
NCT02333162	University of Chicago, IL/USA 2014 - 2028	Phase I	2024-01	Adult patients with AML and high-risk MDS or other hematologic malignancies (18-75 years), before second allogeneic SCT	30	Dose escalation TMI (doses not provided) with fludarabine and melphalan MTD defined as grade 3+ dose-limiting toxicity by CTCAE v 4.0 up to 30 days after second SCT.
NCT05870995	Shanghai Jiao Tong University School of Medicine / China 2023 - 2026	Phase 2	2023-11	Adult patients with R/R AML (16-65 years), before allogeneic SCT	100	TMI (dose not specified, 3 days) in one arm. Cladribine, cytarabine, etoposide, followed by conditioning with fludarabine/busulfan plus either melphalan or TMI, plus venetoclax DFS after 2 years

28 studi di cui 3 randomizzati

2 :TBI vs TMLI 12 Gy in 3 fx ALL in CR (1-17 o 18-65) prima di HSCT aploidentico e da fratello compatibile

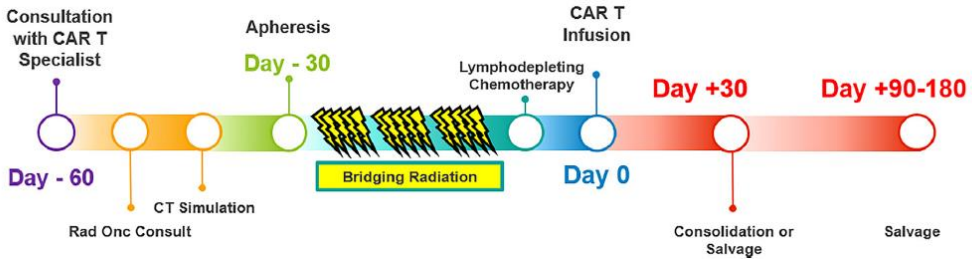
1: Mieloma multiplo

E in fine……..

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The Role of Radiotherapy in Lymphoma Patients Undergoing CAR T Therapy: Past, Present, and Future

Chimeric antigen receptor (CAR) T-cell receptor therapy has transformed outcomes for patients with relapsed and refractory diffuse large B-cell lymphoma (R/R DLBCL). Bridging radiotherapy, defined as radiation delivered between the decision to pursue CARTand infusion of CARTcells, has become an attractive option for patients who would benefit from local disease control or palliation of symptoms. Several potential mechanisms by which radiation therapy may improve CARTefficacy have been proposed that include cytoreduction,tumor debulking,neutralization of immunosuppressive hypoxicand acidic tumor microenvironments,and immunologic and pro-apoptotic synergy between radiation and CART.



Conclusioni

1. In oncoematologia si sono ridotte dosi e volumi
2. Impegno di tecniche IMRT su larga scala
3. L'utilizzo degli IMRT non ha dimostrato un aumento della tossicità tardiva
4. La TBI con VMAT/TOMO ha ridotto le dosi a gli OAR
5. La TBI con VMAT/TOMO approvata dalla COG
6. La TBI-IMRT non si è dimostrata meno immunosoppressiva e meno citolitica rispetto alla 2D
7. Ci sono dati di confronto tra TBI 2D-TBI IMRT solo su studi monocentrici
8. Implementazione della TMI/TMLI come sostituta della TBI con molti studi in corso

Grazie della attenzione