XXXIII CONGRESSO NAZIONALE AIRO

AIRO2023

BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

RE-IRRADIATION: FROM IMRT TO HADRON THERAPY

Elisa D'Angelo
UOC Radioterapia Oncologica Azienda USL di Bologna, Ospedale Bellaria

Associazione Italiana Radioterapia e Oncologia clinica

Reirradiation… a recent history?

- 1926, Lee and Tannenbaum reported their experience with more than 300 patients managed for recurrent inoperable breast cancer at Memorial Hospital, New York
- From 1930, Soiland and Costolow, for cervical cancer, at the Los Angeles Tumor Institute, California: 11% of 1574 pts.
- Between 1936 and 1941, 461 patients were reirradiated for cervical cancer, by Murphy and Schmitz from Roswell Park Memorial Institute, Buffalo, NY.
- Garland and Sisson reported the results of irradiation for lip, tongue, and ear cancer between 1932 and 1948 (San Francisco)
- Zuppinger reported the University of Zurich data with protracted fractionated radiation therapy between 1931 and 1936 in 107 patients with head and neck tumors.22 Of these, 13 (12%) were reirradiated.
- Between 1940 and 1950, selected patients with nasopharyngeal malignancy were reirradiated at the University of California School of Medicine, San Francisco.
- Chu and Hilaris from Memorial Hospital, New York, about brain metastases, which covers 1954 to 1958.

Advances in Radiation Oncology (2017) 2, 176-182
advances in radiation oncology
www.advancesradonc.org

Critical Review

Preserving the legacy of reirradiation: A narrative review of historical publications

Carsten Nieder MD [a,b,*], Johannes A. Langendijk MD [c], Matthias Guckenberger MD [d], Anca L. Grosu MD [e,f]

1920-1970

Reirradiation… a recent history?

- In a textbook from 1965, Kramer provided a summary of the knowledge about reirradiation, including persistent, recurrent, and new primary tumor scenarios. Factors to consider during decision making included the **natural history of the tumor**, its **extent**, the **condition of the normal tissues**, the **details of the previous treatment**, and the **objective** of the proposed reirradiation.
- He recommended that "an **attempt must be made to determine whether the initial course of therapy has failed because of inadequate doses, geographical miss, or radioresistance** of the tumor.
- **Previously irradiated tissues are compromised a priori to some extent, whether this is clinically obvious or not**."

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Critical Review

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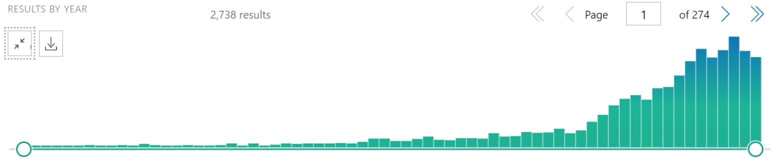
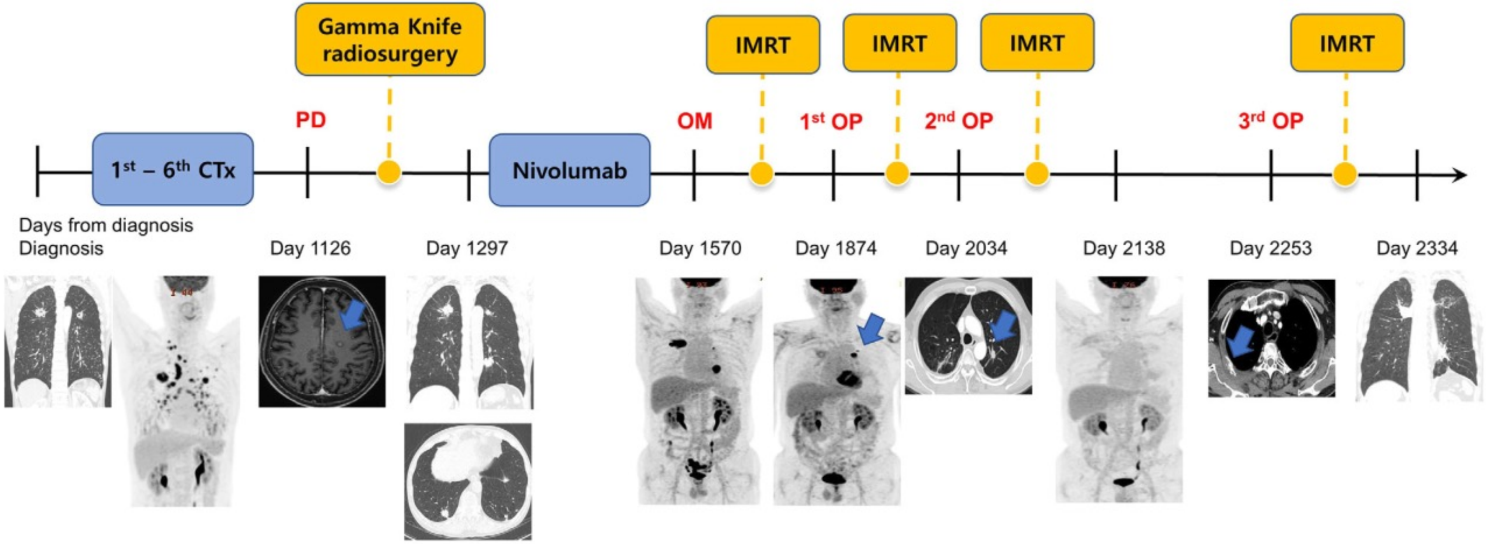
Re-irradiation history



1965

2023

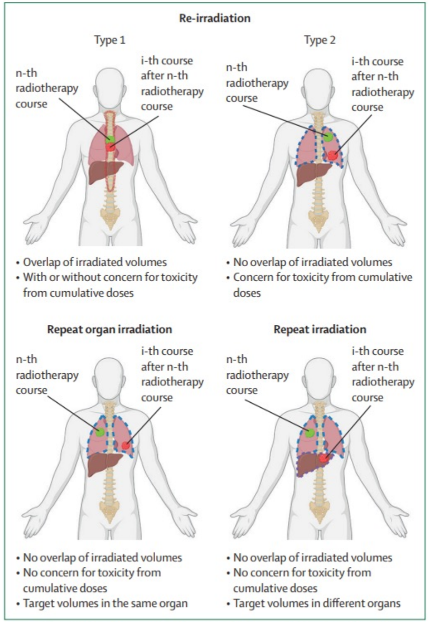
Modern scenario



Definition

European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

Nicolaus Andratschke, Jonas Willmann*, Ane L Appelt, Najlaa Alyamani, Panagiotis Balermpas, Brigitta G Baumert, Coen Hurkmans, Morten Høyer, Johannes A Langendijk, Orit Kaidar-Person, Yvette van der Linden, Icro Meattini, Maximilian Niyazi, Nick Reynaert, Dirk De Ruysscher, Stephanie Tanadini-Lang, Peter Hoskin, Philip Poortmans, Carsten Nieder*



Andratschke 2022

Re-irradiation techniques

European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

Nicolaus Andratschke*, Jonas Willmann*, Ane L Appelt, Najlaa Alyamani, Panagiotis Balermpas, Brigitta G Baumert, Coen Hurkmans, Morten Høyer, Johannes A Langendijk, Orit Kaidar-Person, Yvette van der Linden, Icro Meattini, Maximilian Niyazi, Nick Reynaert, Dirk De Ruysscher, Stephanie Tanadini-Lang, Peter Hoskin, Philip Poortmans, Carsten Nieder

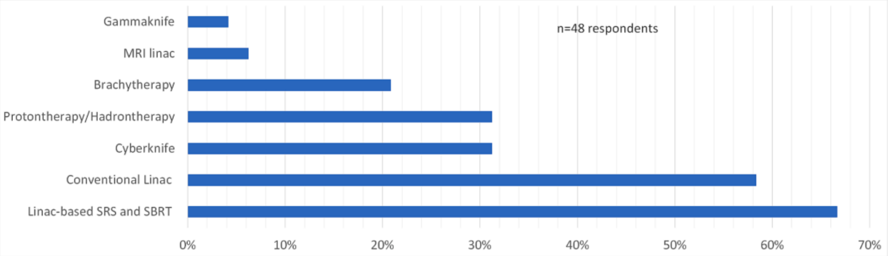
Contents lists available at ScienceDirect
Physica Medica
journal homepage: www.elsevier.com/locate/ejmp

Management of reirradiations: A clinical and technical overview based on a French survey

Myriam Ayadi [a,*], Pauline Dupuis [a], Thomas Baudier [b], Laeticia Padovani [c], David Sarrut [b], Marie-Pierre Sunyach [a]

[a] Radiation Therapy Department, Léon Bérard Centre, Lyon, France
[b] Univ Lyon, INSA-Lyon, Université Lyon 1, CNRS, Inserm, Centre Léon Bérard, CREATIS UMR 5220, U1206, F-69373 Lyon, France
[c] Radiotherapy Department, Assistance Publique des Hôpitaux de Marseille, Marseille, France

- EBRT in 265 (54%) of the studies:
  - 3D CRT(n=75),
  - IMRT or VMAT (n=64)
  - SBRT to cranial (n=46) or extracranial targets (n=80)
- Particle in 39 (8%)
- Brachytherapy 46 (9%)



Re-irradiation number

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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Original Article

Re-irradiation in clinical practice: Results of an international patterns of care survey within the framework of the ESTRO-EORTC E^2-RADIatE platform

Jonas Willmann[a,*], L. Appelt[b], Panagiotis Balermpas[a], G. Baumert[c], Dirk de Ruysscher[d], Morten Hoyer[e], Coen Hurkmans[f], Orit Kaidar-Person[g], Icro Meattini[h,i], Maximilian Niyazi[j,k], Philip Poortmans[l,m], Nick Reynaert[n], Stephanie Tandini-Lang[a], Yvette van der Linden[o], Carsten Nieder[p,q], Nicolaus Andratschke[a]

brain (77%, n = 287)
pelvis (65%, n = 241)
head and neck region (63%, n = 235)
thorax (60%, n = 221)
breast/chest wall (51%, n = 189)
abdomen (39%, n = 145)

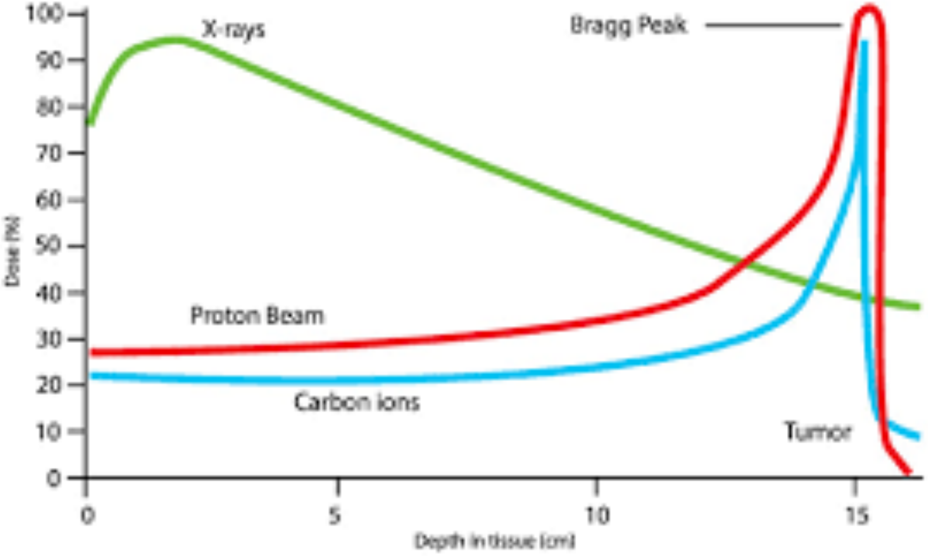
Challenges in reirradiation

Minimize dose to OAR

Efficacy in radioresistance

Dose escalation

Challenges in reirradiation



Brain

Table 1 Selected studies of reirradiation for recurrent glioblastoma

Author	No pts	RT Type	Median Dose (Gy/fr)	Concurrent Systemic Therapy (N)	Interval between RT courses (months)	Median PFS (months)	Median OS (months)	RN (%)
Combs et al., 2005	59	FSRT	36/18	TMZ or PVC, (36)	10	5	8, 23% at 12 months	0
Grosu et al., 2005	34	HSRT	30/6	TMZ (29)	16	NR	8 (both), 11 (RT + TMZ), 6 (RT alone)	20.5
Kong et al., 2008	65	SRS	16/1	None	4.3	4.6	23	37.5
Cuneo et al., 2009	49	SRS	15/1	BEV	20	5.2 (+BEV), 2.1 (-BEV)	11.9 (+BEV), 3(-BEV)	10
Gutin et al., 2009	20	HSRT	30/5	BEV	15	7.3 (4.4–8.9)	12.5; 54% at 12 months	0
Fogh et al., 2010	105	HSRT	35/10	TMZ (26), other (22)	8	NR	11	0.7
Minniti et al., 2011	36	HSRT	37.5/15	TMZ	14	5; 42% at 6 months	9.7; 33% at 12 months	22.2
Minniti et al., 2013	38	HSRT	30/5	TMZ	15.5	6 24% at 12 months	12.4; 53% at 12 months	
Martinez-Carrillo et al., 2014	46	SRS	18/1	NR	10	NR	7.5	10
Wick et al., 2014	91	FSRT	36/18	APG101 (58)	21	2.5 (RT), 4.5 (RT + APG101)	11.5 (both groups)	1.3
Kim H.R. et al., 2015	57	SRS	15/1	TMZ	8.8	3.6 (2.3 + TMZ)	9.2 (15.5 + TMZ)	NR
Minniti et al., 2015	42	HSRT	25/5	FTM (23) BEV (19)	14	50% (BEV), 18% (BEV + FTM) at 6 months	30% (BEV), 8.3% (BEV + FTM) at 12 months	16.6
Pinzi et al., 2015	88	SRS	16–22/1	NR (22)	15	NR	11.5 48% at 12 months	6
Imber et al., 2017	174	SRS	16/1	TMZ (20), CCNU (13), BCNU (11)	8.7	NR	10.6	13
Kim et al., 2017	57	SRS	15/1	TMZ (28)	NR	3.6, 6 (+TMZ)	9.2, 15.5 (+TMZ)	24.4
Sharma et al., 2017	53	SRS	18/1	None	16	4.4	11	4
Palmer et al., 2018	87	SRT	35/10	none	10.8	NR	13.9	NR
Fleischmann et al., 2019	124	FSRT	36/18	BEV (95)	18	5	9	6.9
Scartoni et al., 2020	33	PBRT	36/18	TMZ (7)	21.3	5.9	8.7	9.09
Kaul et al., 2020	133	HSRT	41.8–49.4/12–15	TMZ (58)	14	NR	6	5.6
Saeed et al., 2020	45	PBRT	42.6/20	TMZ (16), BEV (4), TMZ + BEV (10)	20.2	13.9	14.2	8.8
Attia et al., 2022	57	FSRT	36/18	none	16	8	11	3.5
Tsien et al., 2023	170	HSRT	35/10	BEV + RT, BEV alone	NR	54% vs. 29% at 6 months	10.1 BEV + RT, 9.7 BEV alone	0

Legend: BEV, bevacizumab; BCNU, Carmustina; CCNU, Lomustine; FSRT, fractionated stereotactic radiotherapy; FTM, fotemustine; HSRT, hypofractionated stereotactic radiotherapy; NR, not reported; OS, overall survival; PBRT, proton beam radiotherapy; PFS, progression-free survival; PVC, Procarbazine, lomustine, vincristine; RN, radionecrosis; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; TMZ temozolomide

90% glioblastoma local recurrence

Median survival times from 7 to 13 months and 1-year OS rates of 30–55% have been observed following either **SRS** or **fractionated SRT**, with 1-year incidence of neurological toxicities ranging from 5 to 20%

De Pietro, 2023

Brain

First author, year [reference]	Country	Primary tumour	Site	Age	No. patients/ reirradiation courses	Time to reirradiation (median, range)	Tumour volume	Type of study	Total dose first radiotherapy course (Gy: Median, range)	Total dose second radiotherapy course (GyRBE: Median, range)	No. fractions	Dose per fraction (GyRBE)	Local control/ overall survival rates	Acute and late toxicities
Brain														
Saeed, 2022 [13]	USA	GBM	Brain	Adult	45	20 months (3–77)	NS	Prospective	60 (25–60)	46.2 (25–60)	NS	2.2 (1.2 –4)	Median PFS 13.9 months; median OS 14.2 months	AT: 3 grade 3; LT: 4 grade 3
Scartoni, 2020 [14]	Italy	GBM	Brain	Adult	33	21.3 months (5–96)	Median CTV 75 cm^3	Prospective	60	36	18	NS	Median PFS 5.9 months; median OS	AT: 3 grade 2

no comparative studies have demonstrated the clinical superiority of a technique over another in patients with brain tumors in terms of local control and treatment-related toxicity

Brain

Median Dose 46.2 Gy (25-60)

Table 3 Clinical outcomes of proton beam therapy reirradiation patients

Parameter	All patients (N = 45) N	%
Survival, mo (95% confidence interval)		
Median progression-free survival	13.9 (8.2-20)	
Median overall survival	14.2 (9.6-16.9)	
Toxicity, n		
Grade 3, acute	1	2.2%
Grade 3, late	4	8.8%
Grade 4+, any	0	0%

↑ G3 TOX…Dose

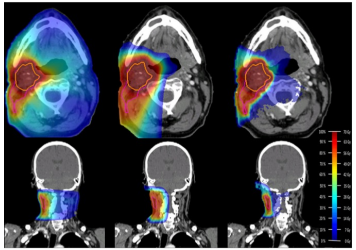
Median Dose 42.3 Gy (30-60)

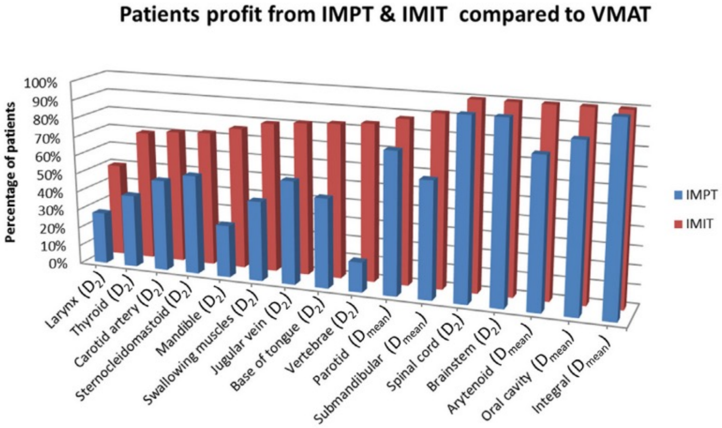
26 patients with recurrent malignant brain tumors treated with conventional radiotherapy (RT, n = 8), stereotactic radiotherapy (SRT, n = 10), and proton beam therapy (PBT, n = 8)

median survival	**18.3 months**
local control	9.3 months
…glioblastoma	
median survival	**13.1 months**
local control	11.0 months

Saaed 2020, Mizumoto 2013

HNSCC



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Particle re-irradiation

Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric *in silico* ROCOCO trial

Daniëlle B.P. Eekers[a,*], Erik Roelofs[a], Urszula Jelen[b,1], Maura Kirk[c], Marlies Granzier[a], Filippo Ammazzalorso[b,1], Peter H. Ahn[c], Geert O.R.J. Janssens[d], Frank J.P. Hoebers[a], Tobias Friedmann[b,1], Timothy Solberg[c], Sean Walsh[a], Esther G.C. Troost[a,e,f,g], Johannes H.A.M. Kaanders[d], Philippe Lambin[a]

[a] Department of Radiation Oncology (MAASTRO), GROW – School for Oncology and Developmental Biology, Maastricht University Medical Centre, The Netherlands; [b] Department of Radiotherapy and Radiation Oncology, University of Marburg, Germany; [c] Hospital of the University of Pennsylvania (UPenn), USA; [d] Department of Radiation Oncology, RadboudUMC, Nijmegen, The Netherlands; [e] Department of Radiation Oncology, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden; [f] Institute of Radiooncology, Helmholtz-Zentrum Dresden-Rossendorf; and [g] German Cancer Consortium (DKTK), Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany

- the exact magnitude of the clinical benefit is uncertain as a decrease in dose does not always translate into a clinically relevant decrease of toxicity risk

HNSCC

24-50% HNSCC local recurrence

- Series 220 pts, 192Ir seeds, on neck and base of the tongue-
  - 2-, 5- and 10-year LC rates of 69%, 51% and 41%
  - one-third of the cohort (60 pts) developed severe late complications
- cohort of 69 patients receiving low-dose BT with 125I and 103Pd after surgery
  - LC rates in 1-, 3- and 5-year follow-ups constituted 55%, 38%, 28%
  - late severe complications high
- 96 patients receiving reRT for rHNC by CyberKnife®
  - High total doses (>40 Gy) proved beneficial as measured by 1-|2-|3-year LC rates: 69.4%|57.8%|51.1%
  - Target volumes < 25 cm3
  - low incidence of radiation complications has been attributed to skip-a-day fractionation
- Vargo et al. published a report (2015) on 48 patients after stereotactic body reRT in combination with cetuximab target therapy
  - smaller tumors (18 pts, 38%) received single focal doses of 8 Gy in 5 fractions to TD of 40 Gy; for tumors ≥ 25 cm3 (30 pts), single doses were increased to 8.8 Gy and delivered also in 5 fractions to TD of 44 Gy
  - Acute radiation reactions grade 3 developed in 3 pts (6%
- The meta-analysis by Lee et al. (2020), encompassing a total of 575 cases from 10 multicenter studies
  - Total dose amounted to 24–44 Gy (median 30 Gy) delivered in 3–6 fractions (median 5
  - The 2-year OS and LC rates constituted, respectively, 30.0% (24.5–36.1%) and 47.3% (3.1–62.1%).

HNSCC

Study	Period	n pts	Follow-Up Time	Histology	Toxicity	LC	OS	DSS/PFS	RT Type
Riaz et al. [64]	1996–2011	348	32.6 m	various	G ≥ 3 | 31.3%	2y 47%	2y 25%	N/d	photons
Langendijk et al. [54]	1997–2003	34	32 m	SCC	G3-4 | 66%	2y 27%	2y 38%; 3y 22%	N/d	photons
Duprez et al. [69]	1997–2011	60	18.5 m	SCC 48; ACC 9; Others 3	Acute: G3 | 35%; G4 | 3% Late: G3 | 11.7%; G4 | 26.7%; G5 | 6.7%	1y 64%; 2y 48%; 5y 32%	1y 44%; 2y 32%; 5y 22%	N/d	photons
Takiar et al. [63]	1999–2014	227	SCC 22.5 m; others 74.7 m	SCC 173; Other 33	G3 | 35.4%	2y 59%	2y 51%	N/d	photons
Langer et al. [58]	2000–2003	99	23.6 m	SCC	Acute: G3 | 49% G4 | 23% G5 | 5% Late: G3 | 16.9% G4 | 16.9% G5 | 3.6%	N/d	1y 50.2%; 2y 25.9%	N/d	photons, CT
Loimu et al. [14]	2000–2007	237	51 m	SCC	Late: G3 | 24%	2y 84%	2y 82%	2y 89%	photons
Platteaux et al. [55]	2000–2009	51	9.5 m	SCC	Acute: G3 | 29.4% Late: G3 | 35.3%	2y 32%	2y 30%	2y 28%	photons
Kharofa et al. [52]	2001–2009	38	16 m	SCC	N/d	N/d	1y 54%; 3y 31%; 5y 20%	N/d	photons, CT
Qiu et al. [65]	2003–2009	70	25 m	SCC	N/d	2y 65.8%	2y 67.4%	N/d	photons
Kong et al. [66]	2009–2014	77	25.7 m	SCC	Late: G ≥ 3 | 64.9%	N/d	1y 92%; 2y 68%; 3y 51.5%	1y 78.7%; 2y 45.5%; 3y 32.3%	photons
Ling et al. [43]	2002–2013	291	9.8 m	255 SCC; 35 ACC; 31 others	Acute: G ≥ 3 | 11.3% Late: G ≥ 3 | 18.9%	N/d	1y 41.4%; 3y 16.6%; 5y 10.8%	N/d	photons, SBRT
Rwigema et al. [42]	2003–2008	96	14 m	SCC	Acute: G3 | 5.2% Late: G3 | 3.1%	TD 40-50Gy: 1y 69.4%; 2y 57.8%; 3y 41.1%. TD 15-36 Gy: 1y 51.9%; 2y 31.7%; 3y 15.9%	all groups: 1y 58.9%; 2y 28.4%	N/d	photons, SBRT
Cengiz et al. [45]	2007–2009	46	N/d	30 SCC; 16 others	G3 | 4.4%	1y—83.8%	1y–47%	N/d	photons, SBRT
Vargo et al. [48]	2007–2013	IMRT 217; SBRT 197	IMRT 8.4 m; SBRT 7.1 m	IMRT SCC 205; SBRT SCC 194; others: 12 IMRT; 3 SBRT	IMRT G3 | 16.6%; SBRT G3 | 11.7%;	N/d	IMRT 2y 35.4%; SBRT 2y 16.3%	N/d	photons, IMRT vs. SBRT

Study	Period	n pts	Follow-Up Time	Histology	Toxicity	LC	OS	DSS/PFS	RT Type
Saroja et al. [111]	1976–1985	46	9.3 m	various, non-SCC	G3 | 25%	2 y 50%	2y 78%	2y 44%	FNT
McDonald et al. [97]	2004–2014	61	29 m	SCC 37; Other 24	G3 | 13.1%; G4 | 3.3%; G5 | 4.9%	2y 19.7%	2y 32.7%	N/d	PT
Beddok et al. [100]	2012–2019	55	41.3 m	SCC	N/d	2y 18.3%	2y 42.5%	N/d	PT + photons
Romesser et al. [96]	2011–2014	92	13.3 m	52 SCC; 9 ACC; 31 others	Acute: G ≥ 3 | 31.4% Late: G ≥ 3 | 15.8%	1y 25.1%	1y 65.2%	1y 84%	PT
Phan et al. [95]	2011–2015	60	13.6 m	SCC	Acute: G3 | 30% Late: G3 | 16.7%	1y 68.4%	1y 83.8%	1y 60.1%	PT
Dionosi et al. [98] et al.	2015–2018	17	10 m	SCC	G3 | 23.5%	1.5y 66.6%	1.5y 54.4%	N/d	PT
Lee et al. [101]	2013–2020	242	N/d	SCC	Acute: G3 | 30.2%; G4 | 62.4% Late: G3 | 32.6%; G4 | 1.6%; G5 | 2%	Fx group 1y 71.8%; quad shot group 1y 61.6	Fx group 1y 66.6%; quad shot group 1y 28.5%	N/d	PT
Kankaanranta et al. [114]	2003–2008	30	N/d	29 SCC; 1 sarcoma	Acute: G3 | 86% Late: G3 | 20%	1y 95% 2y 27%	2y 30%	N/d	NCT
Wang et al. [116]	2010–2013	17	19.7 m	11 SCC; 6 others	G3 | 9%	2y 28%	2y 47%	N/d	NCT
Hirose et al. [118]	2016–2018	21	24.2 m	8 SCC; 13 others	Acute: G3-4 | 10%	N/d	SCC 2y 58%; non-SCC 2y 100%	N/d	NCT
Hayashi et al. [120]	2007–2016	48	27 m	various, non-SCC	G3 | 25%; G4 | 25%; G5 | 2%	2y 40.5%	2y 59.6%	2y 29.4%	CIT
Held et al. [123]	2010–2017	229	28.5 m	124 ACC; 60 SCC; 45 others	Acute: G ≥ 3 | 2.3% Late: G ≥ 3 | 8%	1y 60%; 1.5y 44.7%	26 m	N/d	CIT
Vischioni et al. [121]	2013–2020	15	22 m	7 ACC; 2 SCC; 6 others	Acute: G3–G4 | 6.7%	1y 44%; 2y 35.2%	1y 92.9%; 2y 78.6%; 3y 38.2%	N/d	CIT
Gao et al. [122]	2015–2017	141	14.7 m	106 SCC; 10 ACC; 25 others	Acute: G5 | 0.7% Late: G ≥ 3 | 10.6%	1y 84.9%	1y 95.9%	1y 95.9%	CIT

HNSCC

- Relative Biological Effectiveness of Protons versus Photons in HNSCC
- LET-Based Optimization of Proton Treatment Plans for HNSCC
- Mechanisms Underlying the Enhanced Biological Effects of Proton versus Photon Radiation in Head and Neck Cancer
  - Proton- versus Photon-Induced Changes in Gene and Protein Expression in HNSCC
  - Proton- versus Photon-Induced DNA Damage and Repair in HNSCC
  - Mechanisms Underlying Proton- versus Photon-Induced HNSCC Cell Death
  - Effects of Protons versus Photons on Immune-Related Responses in HNSCC

INTERNATIONAL JOURNAL of PARTICLE THERAPY

The Biological Basis for Enhanced Effects of Proton Radiation Therapy Relative to Photon Radiation Therapy for Head and Neck Squamous Cell Carcinoma

Li Wang, MD, PhD[1]; Piero Fossati, MD[2]; Harald Paganetti, PhD[3]; Li Ma, PhD[1]; Maura Gillison, MD, PhD[4]; Jeffrey N. Myers, MD, PhD[5]; Eugen Hug, MD[2]; Steven J. Frank, MD[6]

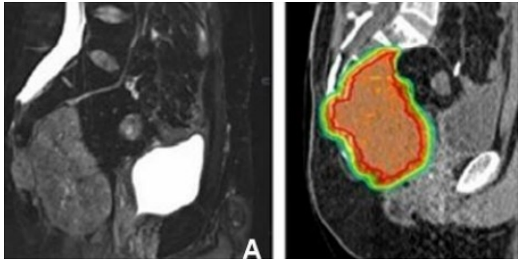
Rectal cancer

4-8% recurrence

Author	N° Patients	Country	Year	Study Design	Study Period	Patient Population	Re-RT Technique	Age, (Range) Years	Previous RT Dose (Range), Gy	Interval between RT (Range), mo	Re-RT Total Dose, Gy	Re-RT Fx. Dose, Gy	CTx. Rate (%) (Agent)	Surgery
Chung SY	35	Japan-Korea	2022	R	2005–2019	LRRC	CIRT	62 (37–76)	50 (20–66)	NR	70.4 Gy (RBE) 101.38 Gy in BED10	4.4 Gy [RBE]	Not admin-istered	0%
	31						29% 3D RT, 71% IMRT or Cyberknife	60 (35–87)	50.4 (45–60)	NR	50 Gy (range 25–62.5 Gy) 60 Gy in BED10		68% *	23% After, 13% Before re-RT
Yamada S	77	Japan	2022	R	2005–2017	LLRC	CIRT	60 (37–76)	50 (20–74)	50 (13–157)	70.4 Gy (RBE)	4.4 Gy [RBE]	Not admin-istered	0%
Barcellini A	14	Italy	2020	R		LRRC	CIRT	58.5 (34–78)	45 (45–76)	65 (14–139)	60 Gy RBE (35–76.8)	3 Gy RBE (3–4.8)	NR	0%
Habermehl D	19	Germany	2014	R	2010–2013	Unresectable LRRC	CIRT	62 (14–76)	50.4 (50.4–60.4)	47.4 (17–110)	36 to 51 Gy (RBE)	3 Gy (RBE).	NR	NR
Cai G.	22	China	2014	Phase II	2007–2012	Unresectable LRRC	IMRT	53 (40–68)	48.6 (36–62)	30 (18–93)	39	1.3 BID	81.8% (5-FU based)	0%
Dagoglu N.	18	Turkey	2015	R	2006–2012	Pelvic RRC or CC	Cyberknife	68 (32–93)	50.4 (25–100.4)	22 (15–336)	25 (24–40)	5	Not admin-istered	NR
DeFoe S.G.	14	USA	2011	R	2003–2008	Presacral RRC	Cyberknife	65.5 (42–77)	50.4 (20–81)	NR	16 (12–36)	12	NR	NR

Mantello G, 2023

Rectal cancer



in vivo 34: 1547-1553 (2020)
doi:10.21873/invivo.11944

Re-irradiation With Carbon Ion Radiotherapy for Pelvic Rectal Cancer Recurrences in Patients Previously Irradiated to the Pelvis

AMELIA BARCELLINI[1*], VIVIANA VITOLO[1*], LORENZO COBIANCHI[2,3], ANDREA PELOSO[4,5], ALESSANDRO VANOLI[6], ALFREDO MIRANDOLA[1], ANGELICA FACOETTI[1], MARIA ROSARIA FIORE[1], ALBERTO IANNALFI[1], BARBARA VISCHIONI[1], FRANCESCO CUCCIA[7], SARA RONCHI[1], MARIA BONORA[1], GIULIA RIVA[1], RACHELE PETRUCCI[1], EMMA D'IPPOLITO[1], FRANCESCA DAL MAS[8,9], LORENZO PREDA[1,2] and FRANCESCA VALVO[1]

- median total CIRT dose was 60 Gy RBE (range=35-76.8)
- median follow-up was 18 months
- 1 year LC 78%; 2 years 52%
- acute toxicities were grade 2 (G2) (7%) and G1 (14%) neuropathic pain. The major late toxicities consisted of G2 peripheral neuropathy (14%)

Rectal cancer

Ann Surg Oncol (2022) 29:99–106
https://doi.org/10.1245/s10434-021-10876-4

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

Carbon Ion Radiotherapy for Locally Recurrent Rectal Cancer of Patients with Prior Pelvic Irradiation

Shigeru Yamada, MD, PhD[1], Hirotoshi Takiyama, MD, PhD[1], Yuka Isozaki, MD, PhD[1], Makoto Shinoto, MD, PhD[1], Daniel K. Ebner, MD, MPH[1], Masashi Koto, MD, PhD[1], Hiroshi Tsuji, MD, PhD[1], Hideaki Miyauchi, MD, PhD[2], Mitsugu Sekimoto, MD, PhD[3], Hideki Ueno, MD, PhD[4], Michio Itabashi, MD, PhD[5], Masataka Ikeda, MD, PhD[6], Hisahiro Matsubara, MD, PhD[2], and for the Working Group on Locally Recurrent Rectal Cancer

- 77 pts.
- Dose 70.4 Gy (RBE) (4.4 Gy [RBE] per fraction; 16 fr.
- LC 90% at 3 years and 87% t 5-years

	Acute						Late					
	G0	G1	G2	G3	G4	Total	G0	G1	G2	G3	G4	Total
Skin	23	51	3	0	0	77	25	48	3	1	0	77
GI	52	9	6	0	0	77	66	1	1	9	0	77
GU	70	2	5	0	0	77	73	0	4	0	0	77
Infection	64	5	3	5	0	77	60	1	3	13	0	77
Pain	36	23	16	2	0	77	35	24	16	2	0	77
Neuropathy	39	28	9	1	0	77	33	23	17	4	0	77

10% G3 acute tox
21% G3 late tox

Rectal cancer

Author	Re-RT Technique	Follow up (Range), Months	Progression-Free Survival (PFS)					Overall Survival (OS)					Local Control (LC)				
			Median (months)	1-year PFS	2-year PFS	3-year PFS	5-year PFS	Median (months)	1-year OS	2-year OS	3-year OS	5-year OS	Median (months)	1-year LC	2-year LC	3-year LC	5-year LC
Chung S.Y.	CIRT	45.7 (7–148.4)	NR	NR	NR	NR	NR	Not achieved	97%	93%	86.4%	62%	NR	94%	NR	87%	70%
	3D—IMRT or Cyberknife	22.8 (7.2–148.4)	NR	NR	NR	NR	NR	36.9	88.9%	59%	54.5%	30%	NR	89%	NR	44%	55%
Yamada S.	CIRT	45 (7–159)	14	58%	36%	33%	25%	47	90%	73%	61%	38%	NR	85%	75%	69%	62%
Barcellini A.	CIRT	18	m-PFS 14.4 (2–40)	64.3%	43%	NR	NR	NR	100%	76.2%	76.2%	NR	14.5 (2.4–49.5)	78%	52%	NR	NR
Habermehl D.	CIRT	8	NR	NR	NR	NR	NR	9.1	NR	NR	NR	NR	20.6 *	85%	NR	NR	NR
Cai G.	IMRT	17 (2–59)	NR	67%	10.7%	NR	NR	19	85.9%	27.2%	NR	NR	14	NR	NR	NR	NR
Dagoglu N.	IMRT	38 (6–36)	38	80.2%	68.7%	61.1%	NR	40	76.8%	65.9%	59.3%	NR	NR	100%	93.7%	85.9%	NR
DeFoe S.G.	cyberknife	16.5 (6–69)	NR	NR	NR	NR	NR	NR	90%	78.8%	NR	60%	NR	90.9%	68.2%	30%	NR

Mantello G, 2023

Rectal cancer

Study author	Type of study	Study details
Combs et al. (Heidelberg Germany) [18]	Prospective phase I/II study	Locally recurrent rectal cancer with inoperable lesion with prior photon irradiation of 20–60 Gy Time between initial radiotherapy and re-irradiation of at least 12 months Patients will be treated within seven increasing dose regimens starting at 12 × 3 GyE up to 18 × 3 GyE
HIMAT1351 (Japan) [19]	Prospective phase II study	CIRT for patients with local recurrence after primarily resected rectal cancer
Japan [20]	Prospective phase II study	CIRT for pelvic recurrent rectal cancer in patients with prior pelvic CIRT

No comparative studies

PARTICLE THERAPY:
Re-irradiation patients… and QoL

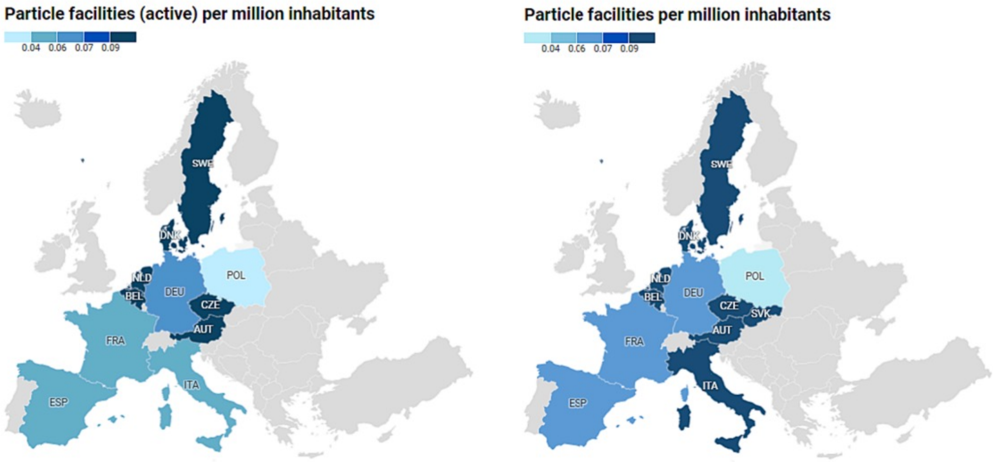


Fig. 2. Density of particle therapy facilities over million inhabitants in the European Union (august 2022) considering (left) active facilities and (2a) total facilities (active, under construction, in planning) (2b). created with https://app.datawrapper.de/.

Reirradiation is performed by all centers in a proportion ranging from < 5% to 20% of cases.

Mazzola GC. et al., 2023

PROTON THERAPY:
Re-irradiation patients… and costs

Brodin *et al. Radiat Oncol* (2021) 16:19
https://doi.org/10.1186/s13014-021-01745-1
Radiation Oncology

RESEARCH Open Access

Individualized quality of life benefit and cost-effectiveness estimates of proton therapy for patients with oropharyngeal cancer

N. Patrik Brodin[1,2*], Rafi Kabarriti[1,2], Clyde B. Schechter[4], Mark Pankuch[3], Vinai Gondi[3], Shalom Kalnicki[2,6], Madhur K. Garg[1,2,5,6] and Wolfgang A. Tomé[1,2,7*]

Normal tissue complication	Management/patient procedure	Estimated cost	Reference
Oral mucositis (grade ≥ 3) or Esophagitis (grade ≥ 3)	Fentanyl 25 μg/h patch (for 6 weeks)	$168.8	NADAC database
	Percocet 325 mg tablet (for 6 weeks)	$1514.1	NADAC database
	Mucositis cocktail (for 6 weeks)	$37.0	NADAC database
	Weekly IV hydration (for 4 weeks)	$154.2	2019 Medicare Coding and Payment Report
	PEG tube placement in 30% of cases	$5686*	Callahan et al. [18]
	Emergency room visit in 15% of cases for oral mucositis and 10% of cases for esophagitis	$2096	2018 Health Care Cost and Utilization Report†
	In patient hospitalization in 10% of cases	$19,672	2018 Health Care Cost and Utilization Report
	Loss of 1 month of work	$2718	US Census Bureau Median per Capita Income 2014–2018‡
Dysphagia (grade ≥ 2)	Chronic PEG tube in 10% of cases	$18,836/year*	Callahan et al. [18]
	Stricture dilation in 16% of patients [14, 15]	$1700 (based on average Medicare charges ranging from $1200 to $2200)	www.howmuchisit.org/esophageal-dilation-cost/ (updated Aug 2018)

WHEN?

Camera dei deputati
Servizio Studi
XVIII Legislatura

I nuovi Livelli essenziali di assistenza (LEA)

29 settembre 2022

Dopo essere stato sottoposto al parere delle Commissioni parlamentari competenti, è stato approvato il D.P.C.M 12 gennaio 2017 *Definizione e aggiornamento dei livelli essenziali di assistenza, di cui all'articolo 1, comma 7, del decreto legislativo 30 dicembre 1992, n. 502*, pubblicato sulla G.U. n. 65 del 18 marzo 2017. I precedenti LEA erano stati definiti con D.P.C.M. del 29 novembre 2001.

REIRRADIAZIONE

ASTRO Model Policies

PROTON BEAM THERAPY (PBT)

This Model Policy* addresses coverage for Proton Beam Therapy.

Group 1

Based on the medical necessity requirements and published clinical data that meets the selection criteria above, disease sites that frequently support the use of PBT include the following:

GENERAL
Benign or malignant tumors or hematologic malignancies in children aged 21 years and younger treated with curative intent and occasionally palliative intent treatment of childhood tumors when at least one of the three criteria noted above under "indications for coverage" apply
Benign or malignant tumors or hematologic malignancies in the adolescent/young adult (AYA) population aged 22 years to 39 years treated with curative intent when at least one of the three criteria noted above under "indications for coverage" apply
Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients, deleterious ATM mutations, Li-Fraumeni, retinoblastoma patients, and patients with known or suspected genetic mutations. In addition, patients with other genetic mutations who are at increased risk of developing second cancers at or near the same body location such as but not limited to BRCA 1/2, Lynch syndrome, etc.
Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery
Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)
Primary malignant or benign bone tumors

Prospective Randomized Study in re-irradiation

Strahlentherapie und Onkologie (2023) 199:787–797
https://doi.org/10.1007/s00066-023-02118-1

REVIEW ARTICLE

Prospective randomized clinical studies involving reirradiation: update of a systematic review

Carsten Nieder[1,2] · Jonas Willmann[3] · Nicolaus H. Andratschke[3]

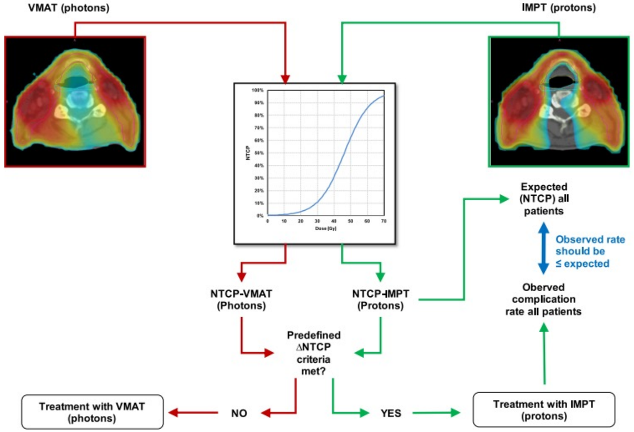
Received: 13 April 2023 / Accepted: 4 July 2023 / Published online: 27 July 2023

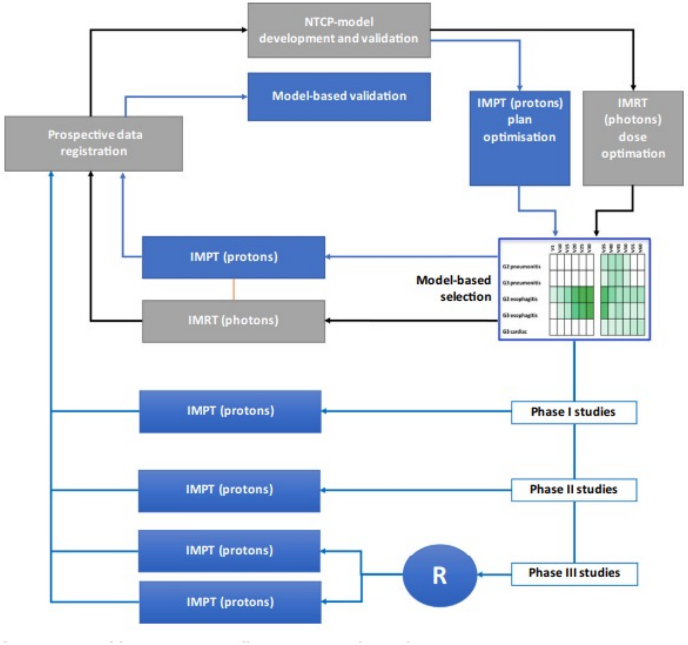
Author and year of publication	Disease site	Study type, inclusion	Arms, design, endpoint, statistics	Patient number and characteristics	Median follow-up	Results and comments
Li et al. 2006 [9]	Nasopharynx cancer	Single centre dose escalation, China, 1999–2002	54 Gy followed by 16, 20 or 24 Gy in 4-Gy fractions (3 fractions per week) 4 primary endpoints, power/assumed differences not reported	36, interval ≥ 6 months, N0 M0	27 mo	In each arm 2–3 patients had received induction chemotherapy 3-year recurrence-free survival was best in the 24-Gy boost group, $p = 0.047$ Similar OS, $p = 0.6$ Similar acute and late toxicity rates, but one fatal bleeding event in the 24-Gy boost group, which also had higher incidence of trismus, $p = 0.08$
Tian et al. 2014 [10]	Nasopharynx cancer	Single centre phase 2, China, 2003–2007	IMRT 68 Gy in 34 fractions vs. 60 Gy in 27 fractions Overall survival, 80% power to detect 23% difference	117, KPS ≥ 70, interval > 6 months	25 mo	Longer OS in the 60-Gy arm, $p = 0.06$ Similar PFS Less mucosal necrosis in the 60-Gy arm, $p = 0.02$
Guan et al. 2016 [11]	Nasopharynx cancer	Single centre phase 2, China, 2002–2008	IMRT 60 Gy in 27 fractions alone vs. same RT + concomitant weekly cisplatin Overall survival, 80% power to detect 30% difference	69, KPS ≥ 70, interval > 6 months	35 mo	Longer OS in the combined modality arm, $p = 0.049$ No significant increase in late toxicity, but more haematologic toxicity in the combined modality arm
Liu et al. 2021 [19]	Nasopharynx cancer	Three centres, phase 3, China, 2011–2017	Endoscopic nasopharyngectomy or IMRT 60–70 Gy (2–2.36 Gy per fraction, 5 fractions per week) Overall survival, 80% power and a two-sided 5% significance-level hazard ratio of 0.52	200, KPS ≥ 70, ≥ 12-month disease-free interval between the initial course of radiotherapy and recurrence, age 18–70 years	56 mo	Improved 3-year overall survival after surgery (86% versus 68% in the IMRT group, $p = 0.0015$)
You et al. 2023 [20]	Nasopharynx cancer	Three centres phase 3, China, 2015–2019	IMRT 60 Gy in 27 fractions vs. 65 Gy in 54 fractions (2 fractions per day) Overall survival and severe late complications, 80% power to detect 20% difference (survival) and 24% difference (toxicity grade 3 or more)	144, KPS ≥ 70, interval > 12 months, age 18–65 years, no radiation-induced complications grade ≥ 3	45 mo	Reduced grade 3 or worse late radiation-induced toxicity in the hyperfractionation group (34% versus 57%, $p = 0.02$) Better 3-year overall survival after hyperfractionation (75% versus 55%, $p = 0.01$) 49% of patients in the hyperfractionation group and 46% in the standard fractionation group had locoregional relapse significant differences favouring hyperfractionated radiotherapy in the general quality-of-life domains of global health status, role functioning, and social functioning, and in the symptom burden domains of pain, financial difficulties, and loss of appetite

ELSEVIER
Seminars in RADIATION ONCOLOGY

Clinical Trial Strategies to Compare Protons With Photons

Johannes A. Langendijk, MD, PhD,[*,||] Liesbeth J. Boersma, MD, PhD,[†,||] Coen R.N. Rasch, MD, PhD,[†,||] Marco van Vulpen, MD, PhD,[‡,||] Johannes B. Reitsma, MD, PhD,[§,||] Arjen van der Schaaf, PhD,[*,||] and Ewoud Schuit, PhD[§,||]





Comparison?

Contents lists available at ScienceDirect

Physica Medica

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

ELSEVIER

Management of reirradiations: A clinical and technical overview based on a French survey

Myriam Ayadi [a,*], Pauline Dupuis [a], Thomas Baudier [b], Laeticia Padovani [c], David Sarrut [b], Marie-Pierre Sunyach [a]

[a] Radiation Therapy Department, Léon Bérard Centre, Lyon, France
[b] Univ Lyon, INSA-Lyon, Université Lyon 1, CNRS, Inserm, Centre Léon Bérard, CREATIS UMR 5220, U1206, F-69373 Lyon, France
[c] Radiotherapy Department, Assistance Publique des Hôpitaux de Marseille, Marseille, France

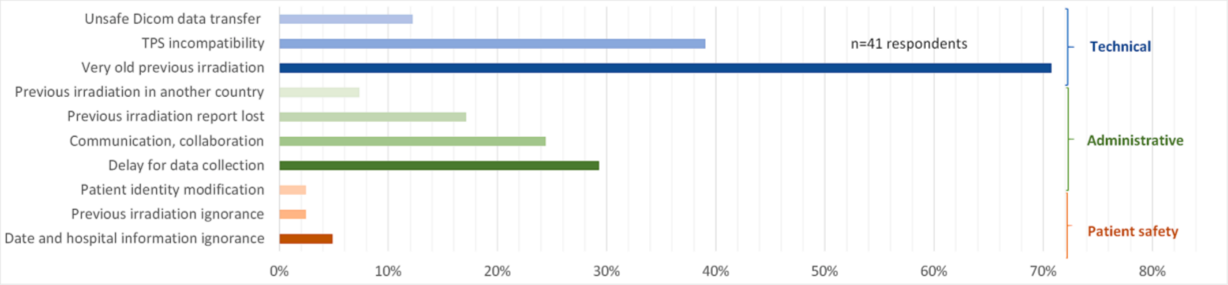
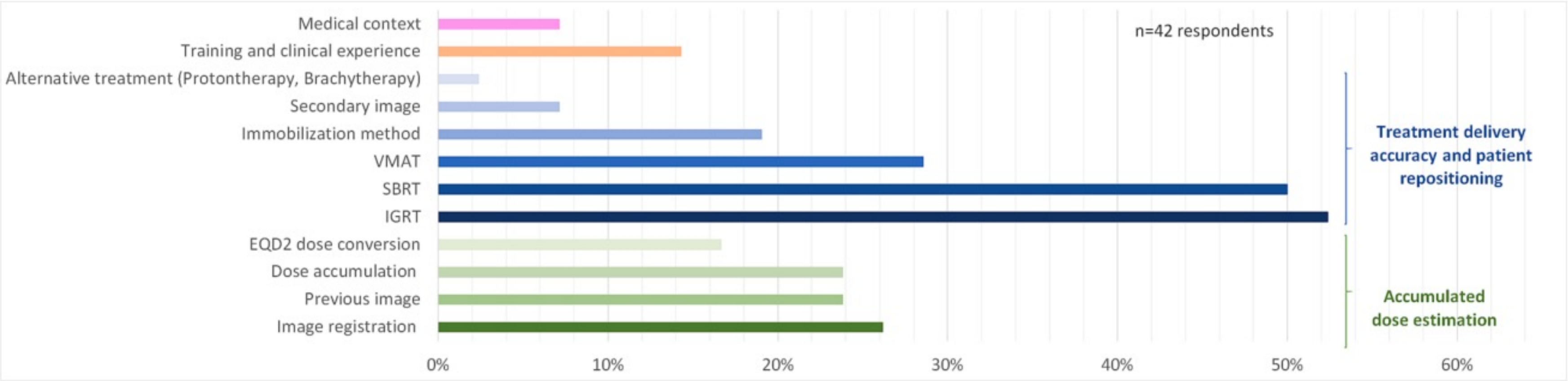


Fig. 1. Difficulties raised by the institutions during the previous irradiation data collection (based on open-ended questions).

European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

Nicolaus Andratschke*, Jonas Willmann*, Ane L Appelt, Najlaa Alyamani, Panagiotis Balermpas, Brigitta G Baumert, Coen Hurkmans, Morten Høyer, Johannes A Langendijk, Orit Kaidar-Person, Yvette van der Linden, Icro Meattini, Maximilian Niyazi, Nick Reynaert, Dirk De Ruysscher, Stephanie Tanadini-Lang, Peter Hoskin, Philip Poortmans, Carsten Nieder

Comparison?



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[c] Radiotherapy Department, Assistance Publique des Hôpitaux de Marseille, Marseille, France

Re-irradiation: Technical, administrative and patient safety

- Issue: previous treatment records that we may receive for patients span a wide range of quality and informations
- Solution? The export of radiation treatment records from commercial planning systems should be standardized
- Issue: diversity of patient data transfer means…
- Solution? Develop a common and secured platform to allow inter-institutional data transfer

Technical, administrative and patient safety

- Issue: DICOM RT planning data transfer inability, due to TPS obsolescence or decommissioning, or incompatible formats
- Solution? TPS vendors should guarantee compatibility of DICOM RT files provided by their software and inversely the ability of software to read DICOM RT files independently of their source

Technical, administrative and patient safety

Issue: Biological and physical dose…

Prioritized wish-list for vendors	Average score
Calculation and visualisation of 3D dose distributions in EQD2 (and/or BED) with organ specific α/β and recovery factors in the TPS	12.7
Calculation of 3D dose distributions in EQD2 (and/or BED) in the TPS	10.11
Reliable deformable image registration	10.04
Visualisation of 3D dose distributions in EQD2 (and/or BED) in the TPS	9.63
Visualisation of uncertainty in dose mapping	9.63
Summed dose across treatment courses in EQD2	9.11
Tool to incorporate uncertainties from different parts of the process (image registration, EQD2 calculation, contouring, recovery factors, etc.) into the final dose reporting	8.78
DVH with 'error bars' to visualise uncertainty in dose mapping & summation	8.67
An all-in-one system!	8.52
Ability to do multiple (per-organ) rigid registrations (and dose summations)	8.26

Radiotherapy and Oncology 182 (2023) 109585
Contents lists available at ScienceDirect
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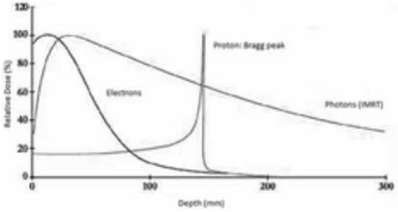
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com
Commentary

Challenges of re-irradiation: A call to arms for physicists - and radiotherapy vendors

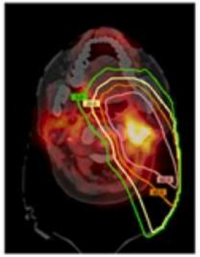
Eliana Vasquez Osorio[a,*], Charles Mayo[b], Andrew Jackson[c], Ane Appelt[d]

Clinical and technical challenges of cancer reirradiation: Words of wisdom

Clinical challenges:
⇒ Patient selection
⇒ Risk/benefit balance
⇒ Multidisciplinary staff meeting



Technical challenges:
⇒ Radiation technique selection
⇒ Target volume definition
⇒ Maximal protection of healthy tissues



Beddok A. et al., 2022

TECHNICAL EVOLUTION

Modern techniques

Evaluation biological effect

Selection of patients

Comparison in the best way

AI for analyse data recorded and correlate to toxicity

"each patient is a special problem to be handled in a special way"