Linfoma di Hodgkin

Oncoematologia e nuove tecniche Radioterapiche

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C.N.R

Pusey W.

Cases of sarcoma and of Hodgkin’s disease treated by exposure to X-rays: a preliminary report.

JAMA 1902; 38:166-169

Radiotherapy “extended field”

R. Gilbert

“Radiotherapy in Hodgkin’s disease. (Malignant Granulomatosis); anatomic and clinical foundations; governing principles; results”

American Journal of Roentgenology 41:198, 1939.

M.V. Peters

“A study of survivals in Hodgkin’s disease treated radiologically”

American Journal of Roentgenology 63:299, 1950.

H.S. Kaplan

“The radical radiotherapy of regionally localized Hodgkin’s disease,”

Radiology 78:553–561, 1962.

Extended fields

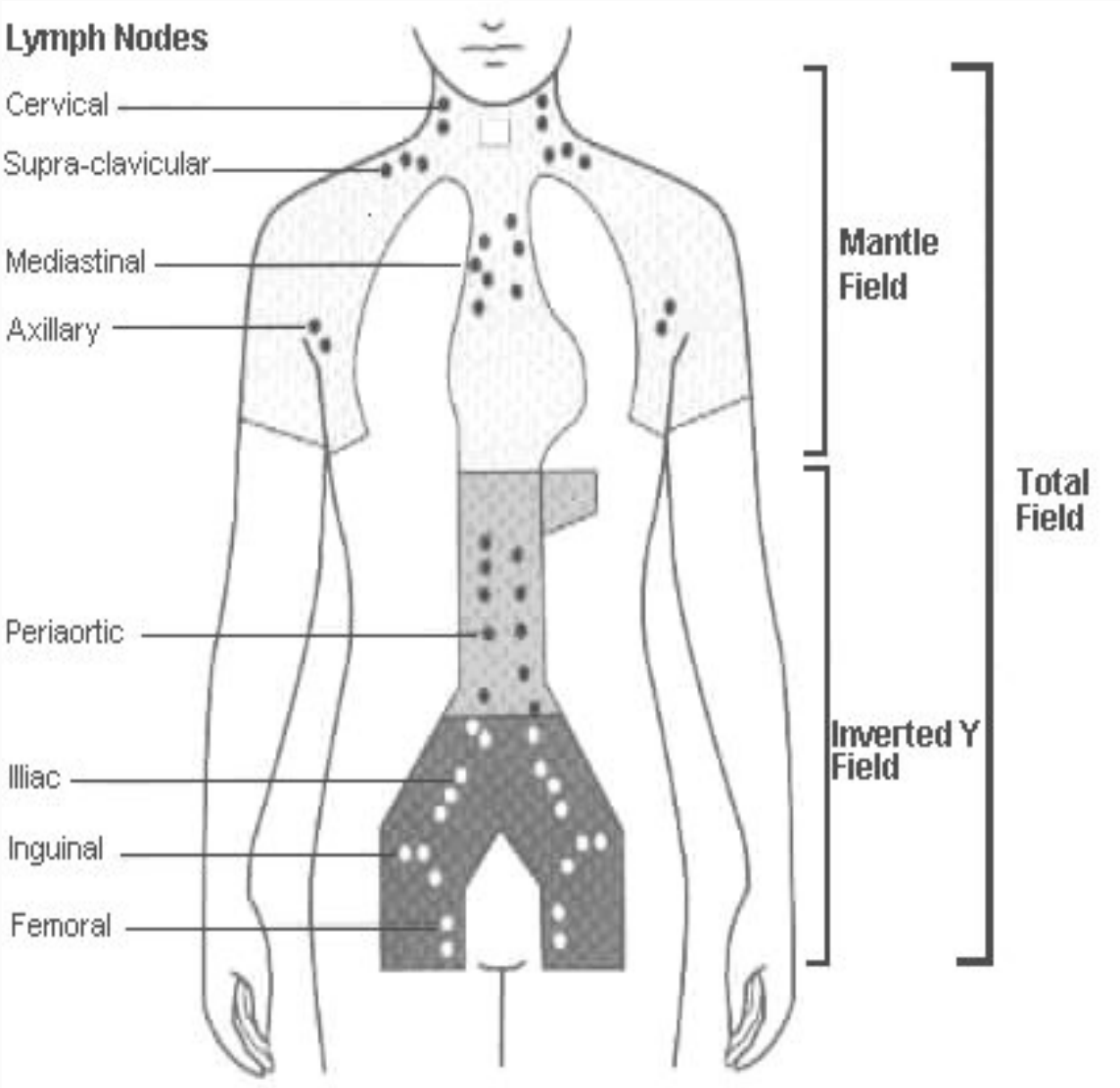
Mantle field → linfonodi sovradiaframmatici

Inverted Y → linfonodi sottodiaframmatici

TLI → Mantle field + Inverted Y

STLI → TLI - pelvi

Yahalom J & Mauch P. Annals of Oncology 13(suppl 1):79-83, 2002


Lymph Nodes
Cervical
Supra-clavicular
Mediastinal
Axillary
Periaortic
Illiac
Inguinal
Femoral
Mantle Field
Inverted Y Field
Total Field

Outcome

Stage I-II

Dose 40 – 45 Gy

DFS 5 year up to 70%

Hoppe RT et Al. Blood 59(3):455-465, 1982
Mauch P et Al. J Clin Oncol 6(10):1576-83, 1988

Chemotherapy in Hodgkin's lymphoma

V. T. Devita Jr., A. A. Serpick, and P. P. Carbone,

"Combination chemotherapy in the treatment of advanced Hodgkin's disease,"

Annals of Internal Medicine 73(6):881–895, 1970.

G. Bonadonna, R. Zucali, and S. Monfardini,

"Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP,"

Cancer 36(19):252–259, 1975.

Late toxicity

- ✓ Lung
- ✓ Heart
- ✓ Thyroid
- ✓ Second cancer

ELSEVIER

European Journal of Cancer 41 (2005) 998–1006

European Journal of Cancer

www.ejconline.com

Survival in Hodgkin's disease patients – Report of 25 years of experience at the Milan Cancer Institute

Gianni Bonadonna *, Simonetta Viviani, Valeria Bonfante, Alessandro M. Gianni, Pinuccia Valagussa

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Available online 24 February 2005

Cause of death at 25 years

- Progressive lymphoma 25.1%
- Chemotherapy related 2.6%
- Second cancers 11.6%
- Potentially treatment related 3.4%

Toxicity of treatment

Prognostic factors

→ Treatment load

→ Irradiated volume

→ Dose

→ Radiation delivery techniques

Early-staged (I-II) unfavourable features (EORTC/GELA)	Early-staged (I-II) unfavourable features (GHSG)
Four or more nodal areas involved	Three or more nodal areas involved
Bulky mediastinum*	Bulky mediastinum*
ESR >50 without B symptoms or >30 with B symptoms	ESR >50 without B symptoms or >30 with B symptoms
Aged 50 years old or more	Extranodal disease

* Bulky mediastinum defined as mediastinal/thoracic ratio >0.35.

Tubiana M et Al. Blood 73(1):47-56, 1989

Diehl V et Al. Med Onc Tum Pharmacother 6(2):155-162, 1989

Haybittle JL et Al. Lancet 1(8453):967-972,1985

✓Chemotherapy exclusion is possible only in the stage IA of nodular lymphocyte predominant HL.

✓Radiotherapy exclusion is possible in large majority of stage III-IV HL patients.

Nogovà L et Al. Annals of Oncology 26(3):434-439, 2008

Symposium article

Annals of Oncology 13 (Supplement 1): 79–83, 2002
DOI: 10.1093/annonc/mdf616

The involved field is back: issues in delineating the radiation field in Hodgkin's disease

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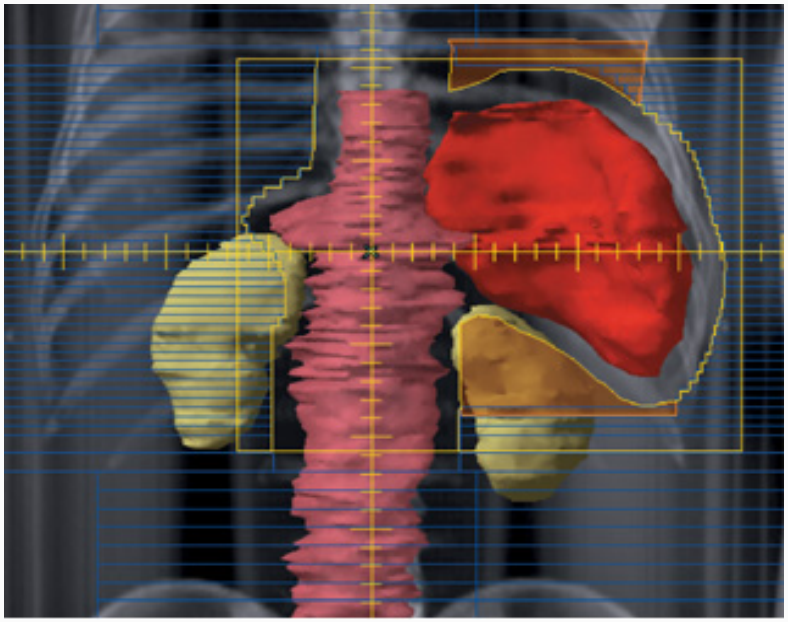
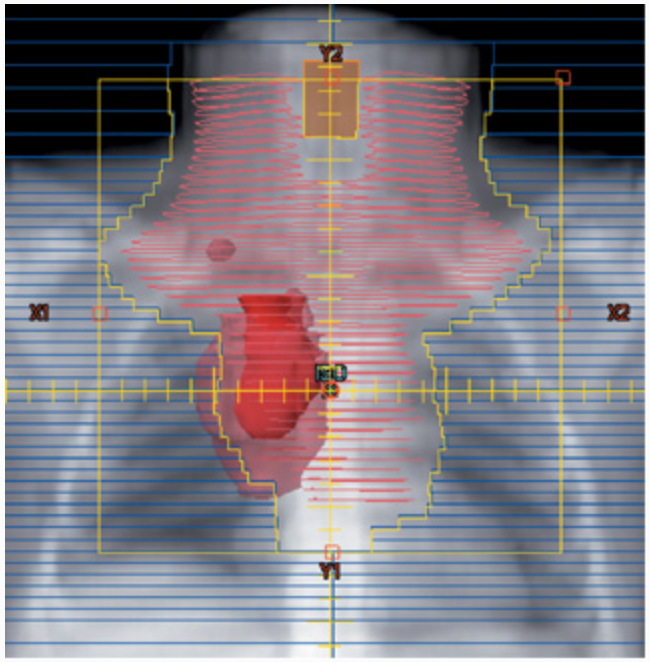




Shaidi M et Al.

Site of relapse after chemotherapy alone for stage I and II Hodgkin's disease.

Radiother Oncol 78(1):1-5, 2006

83% relapses in previous involved site.

Subgroup analysis showed same nodes involved pre-CT

Involved field = extended field?

- Engert , JCO 2003
- Bonadonna, JCO 2004
- Pluetschow, Blood 2005
- Fermè, NEJM 2007

Yes

Involved field=involved node?

Campbell, JCO 2008

May be yes

< Dose

Schewe et Al. IJROBP, 1988

Engert A et Al. N Engl J Med 363:640–652,2010

Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma.

Stage I-II favourable prognosis HL

2 ABVD + 20 Gy IFRT

RT delivery techniques in HL

- ✓3D-Conformal RT
- ✓Field in field (forward IMRT)
- ✓IMRT
- ✓Tomotherapy
- ✓3D-Conformal Proton Therapy

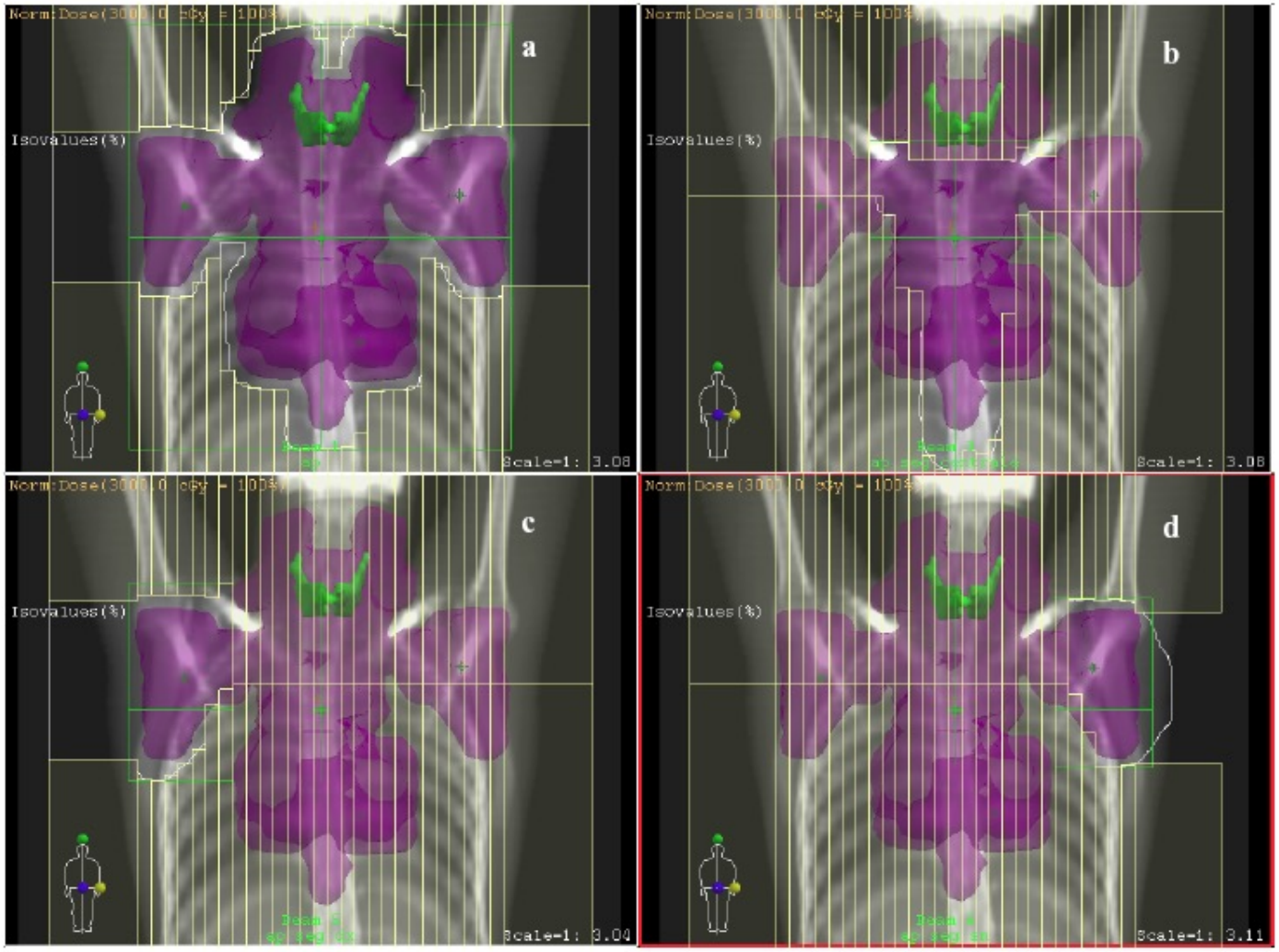
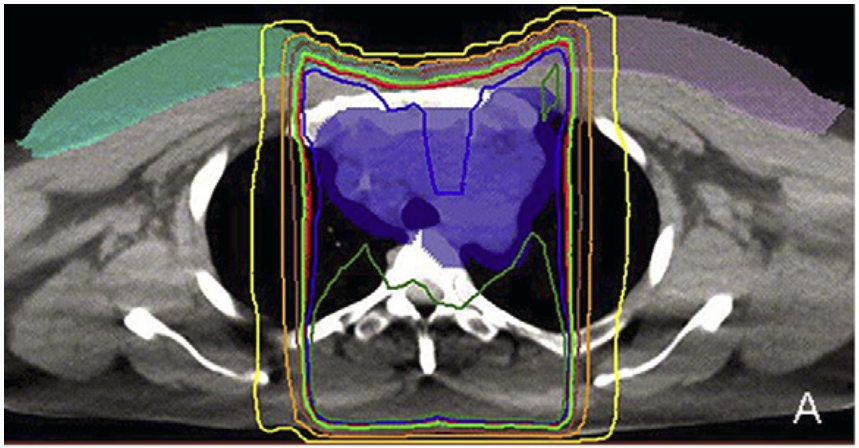
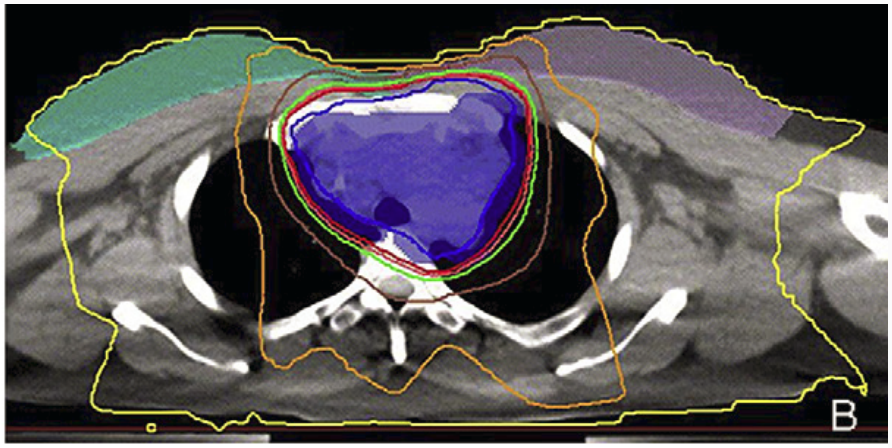
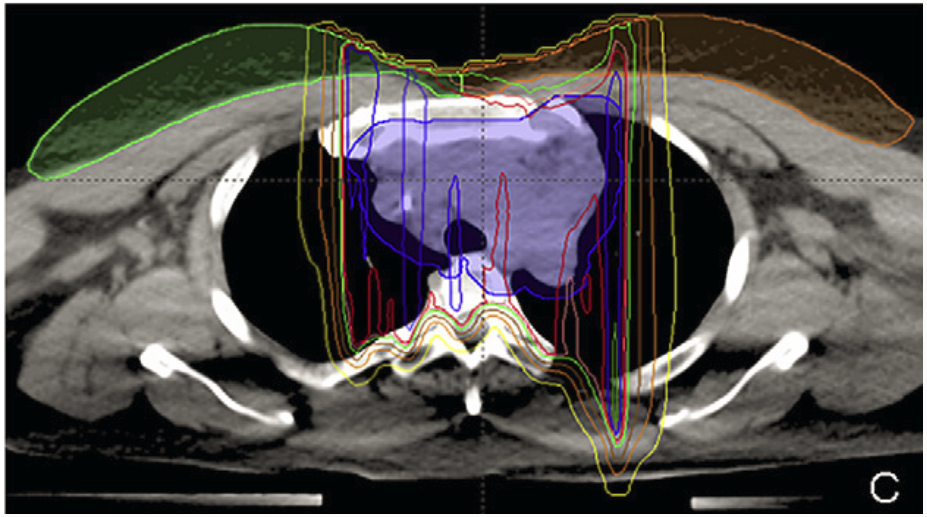
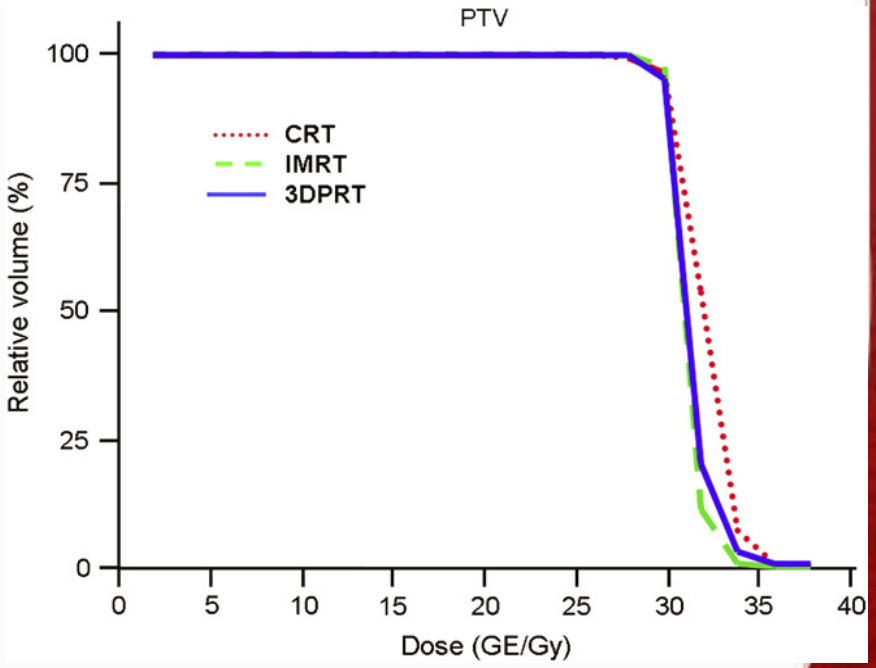


Figure 1 FPIMRT portals. Example of FPIMRT portals: a) main anterior-posterior field (AP); b) central AP subfield; c) right AP axillary subfield; d) left AP axillary subfield. The PTV is shown in magenta color and the thyroid gland in green.









Chera BS et Al. Int. J. Radiation Oncology Biol. Phys. 75(4):1173–1180, 2009

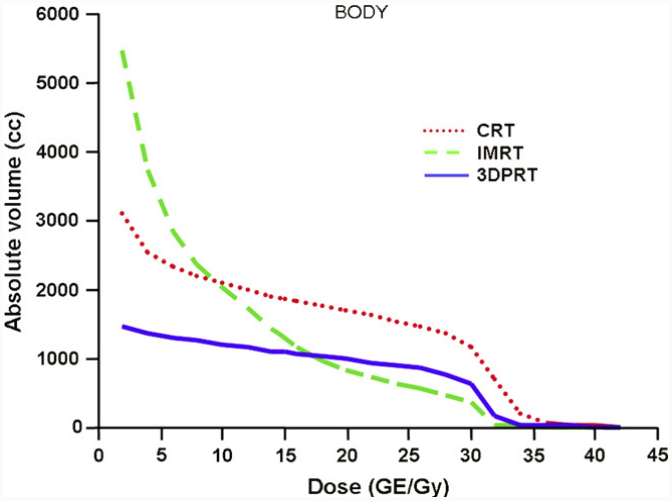
Table 1. Target coverage for CRT, IMRT, and 3D-PRT plans (n = 27 plans) prescribing 30 CGE/Gy to PTV

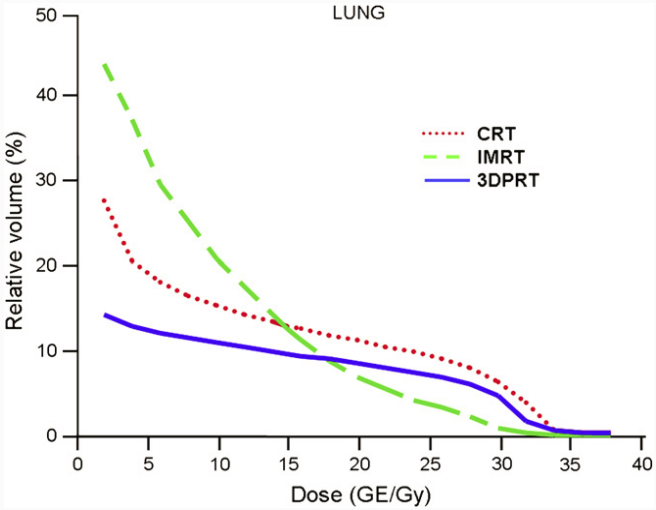
PTV	CRT	IMRT	3D-PRT	Adjusted p
V_{30} (%)	96.49 (1.54)	97.52 (1.92)	95.00 (0.0006)	.003*
Mean dose (CGE/Gy)	31.92 (0.44)	31.37 (0.13)	31.30 (0.84)	.09
Maximal dose (CGE/Gy)	34.15 (0.82)	32.67 (0.52)	33.41 (1.69)	.002*
Minimal dose (CGE/Gy)	28.10 (1.52)	29.14 (1.02)	28.50 (0.98)	.03*

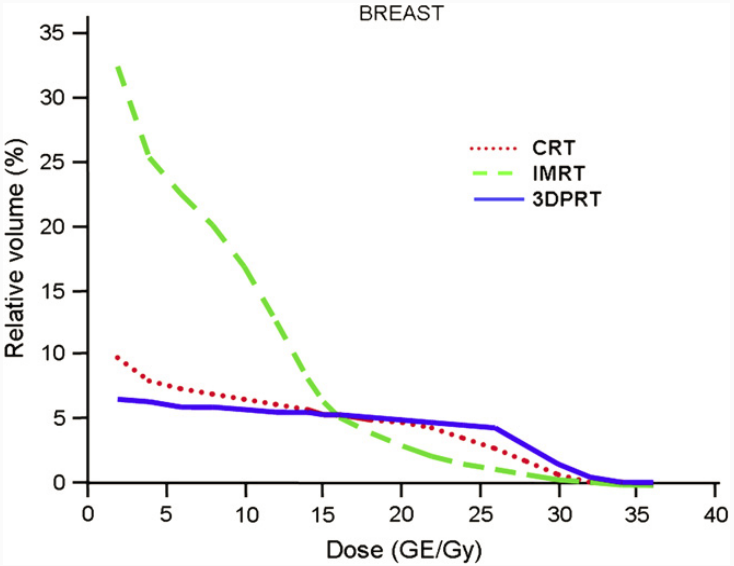
Abbreviations: CRT = conventional radiotherapy; IMRT = intensity-modulated RT; 3D-PRT = three-dimensional proton RT; PTV = planning target volume; V_{30} = relative volume receiving 30 CGE/Gy; CGE = cobalt Gray equivalent.

Data in parentheses are standard deviation.

Chera BS et Al. Int. J. Radiation Oncology Biol. Phys. 75(4):1173–1180, 2009







Chera BS et Al. Int. J. Radiation Oncology Biol. Phys. 75(4):1173–1180, 2009

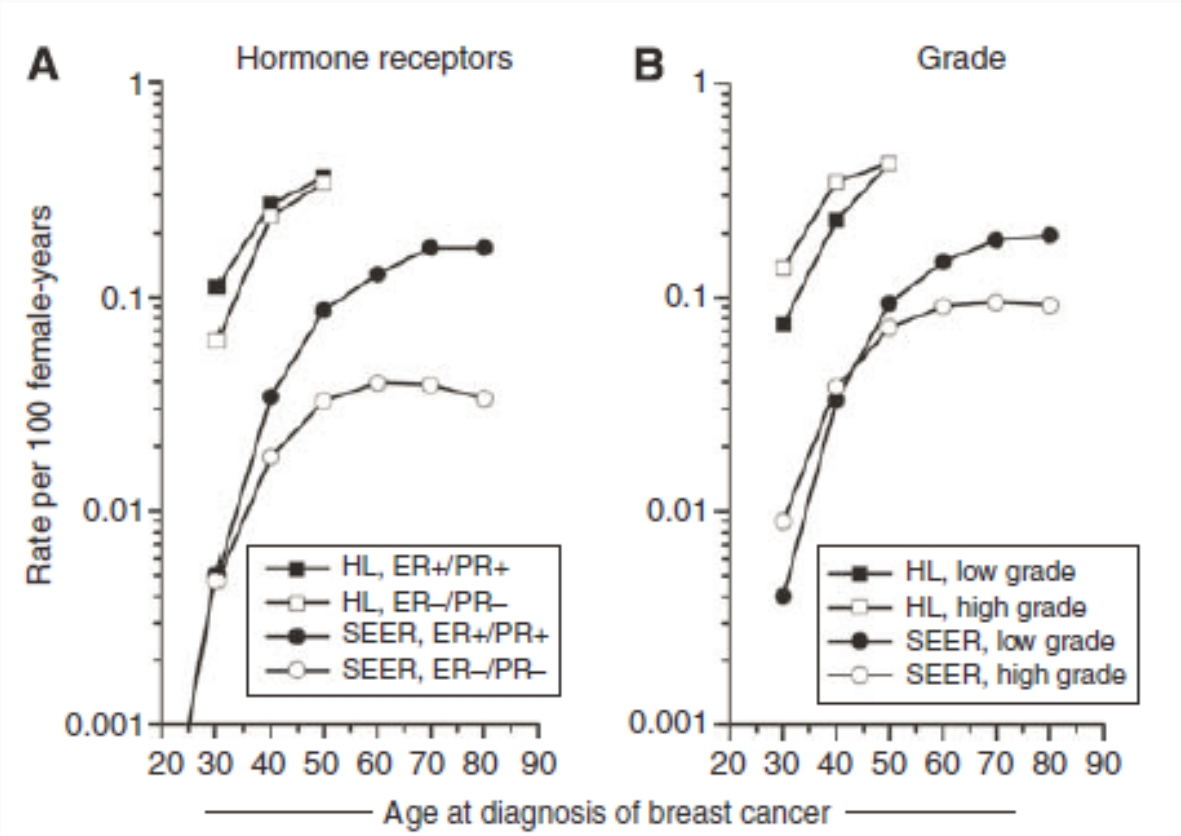
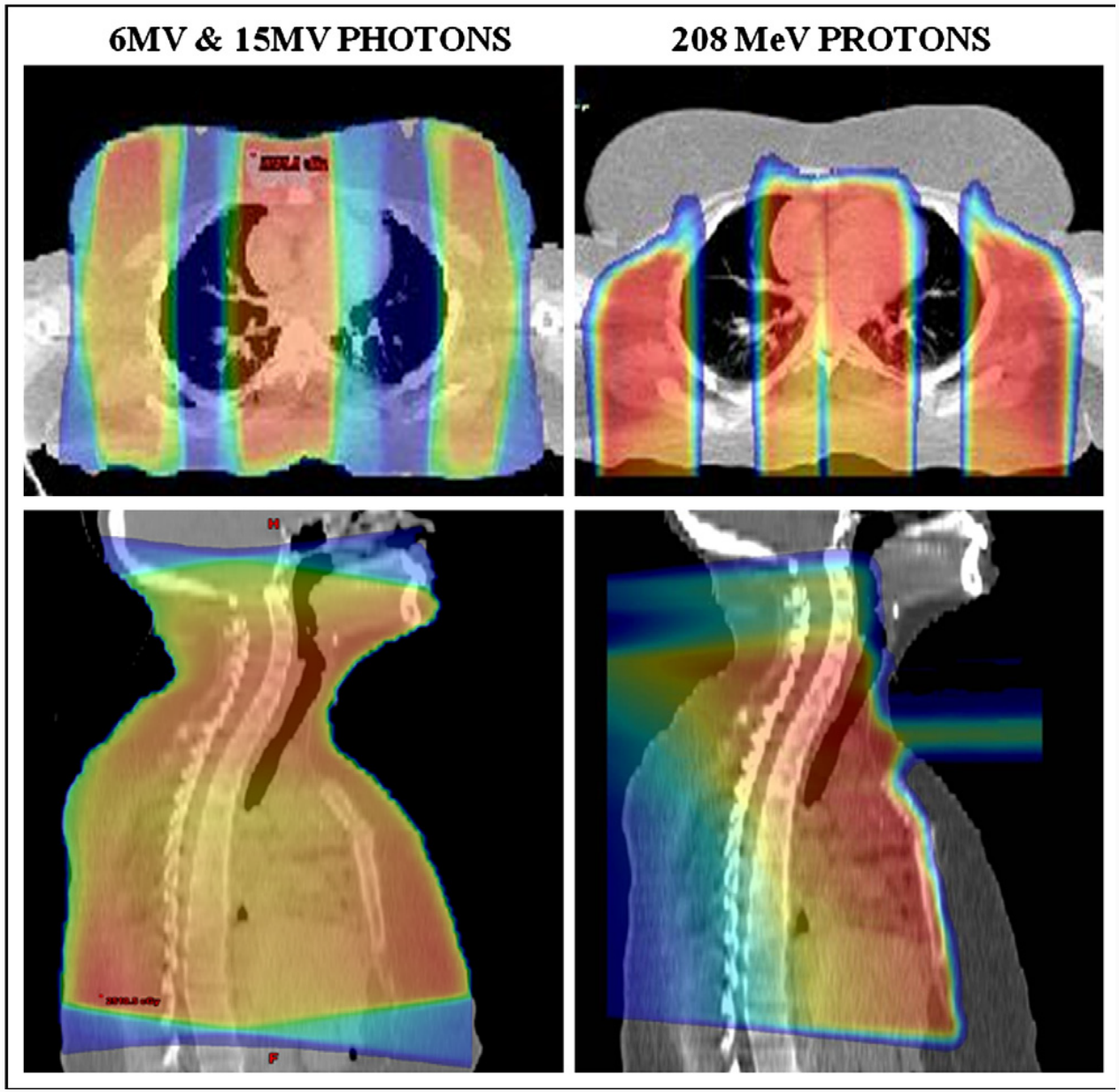


Figure 1 Age-specific incidence rates of female breast cancer (1990–2005) among 5-year survivors of Hodgkin's lymphoma (HL) diagnosed before 35 years of age and treated with radiotherapy and among the general population in nine registry areas of the Surveillance, Epidemiology and End Results (SEER) Programme, (**A**) according to oestrogen-receptor (ER) and progesterone-receptor (PR) status and (**B**) grade.

Dores GM et Al. British Journal of Cancer 103:1081–1084, 2010



Andolino DL et Al. IJROBP, 2011

Table 1. Three-dimensional conformal involved-field photon radiotherapy (3D-CRT)vs.breast-sparing proton therapy (BS-PT):Comparison of patient-specific breast dose

Ann Arbor Stage	Fields treated	Breast size (cm^3)	Breast dose	3D-CRT	BS-PT	Reduction (%)
IIA	L neck, L Sclv, mediastinum	623	Mean dose (Gy/CGE)	0.74	0.14	81
			V5 (cm^3)	23	6	74
			V1 (cm^3)	53	19	64
IIA	R neck, R axilla, B/L Sclv, mediastinum	1150	Mean dose (Gy/CGE)	8.46	2.01	76
			V5 (cm^3)	545	161	70
			V1 (cm^3)	861	299	73
IIA	B/L neck, B/L Sclv, mediastinum, epiphrenic	1302	Mean dose (Gy/CGE)	3.61	0.93	74
			V5 (cm^3)	282	105	63
			V1 (cm^3)	481	183	62
IIA	B/L neck, B/L Sclv, mediastinum,	2364	Mean dose (Gy/CGE)	3.45	0.44	87
			V5 (cm^3)	410	97	76
			V1 (cm^3)	807	195	76
IIB	L neck, L Sclv, mediastinum	600	Mean dose (Gy/CGE)	5.21	1.26	76
			V5 (cm^3)	196	60	69
			V1 (cm^3)	258	109	58
IIAX	L neck, L Sclv, mediastinum	831	Mean dose (Gy/CGE)	1.93	0.37	81
			V5 (cm^3)	95	33	65
			V1 (cm^3)	160	50	69
IIAX	Mantle, epiphrenic	1009	Mean dose (Gy/CGE)	10.15	1.98	80
			V5 (cm^3)	559	163	70
			V1 (cm^3)	836	326	61
IIAX	R neck, B/L Sclv, mediastinum	1575	Mean dose (Gy/CGE)	4.19	0.73	83
			V5 (cm^3)	310	89	71
			V1 (cm^3)	919	193	79
IIBX	B/L neck, B/L Sclv, mediastinum	1067	Mean dose (Gy/CGE)	10.24	0.97	91
			V5 (cm^3)	560	76	86
			V1 (cm^3)	773	313	60
IIBX	Mantle	2741	Mean dose (Gy/CGE)	12.17	0.99	92
			V5 (cm^3)	1771	194	89
			V1 (cm^3)	2741	467	83
			Mean dose (Gy/CGE)	4.70	0.95	80 ($p < 0.001$)*
			V5 (cm^3)	360	93	74 ($p = 0.013$)*
			V1 (cm^3)	790	194	75 ($p = 0.009$)*

Abbreviations: L = left; R = right; B/L = bilateral; Sclv = supraclavicular field; V5 = volume of breast tissue receiving ≥5 Gy; V1 = volume of breast tissue receiving ≥1 Gy.

* Statistically significant.

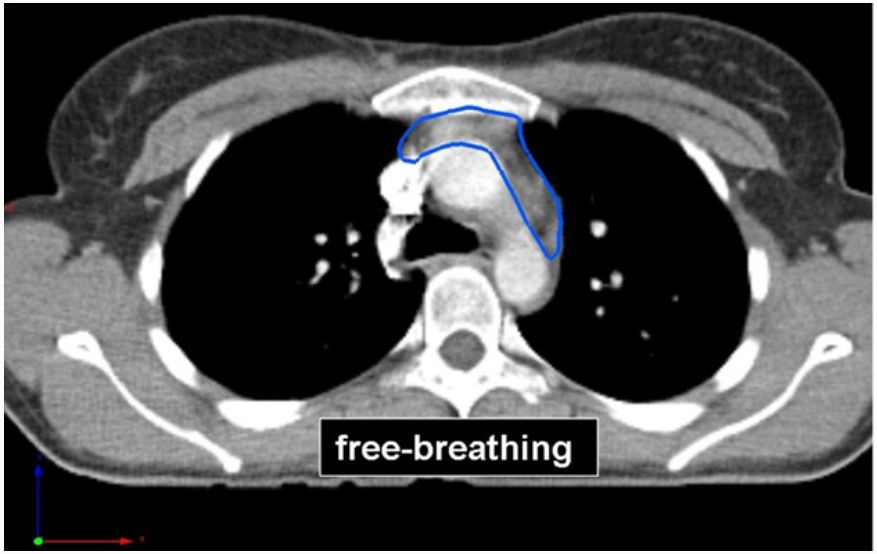
Andolino DL et Al. IJROBP, 2011

Table 2. Three-dimensional conformal involved-field photon radiotherapy (3D-CRT) vs. breast-sparing proton therapy (BS-PT):Comparison of dose to nonbreast organs at risk

Organ at risk	3D-CRT	BS-PT	*p*
Mean lung dose	10.60	9.09	0.037*
Lung V20 (%)	29	26	0.068
Mean heart dose	14.16	17.01	0.082
Maximum heart dose	22.24	22.66	0.280
Mean thyroid dose	21.46	15.79	0.004*
Mean cord dose	11.69	13.92	0.352
Maximumcord dose	22.46	22.16	0.118
Mean esophageal dose	19.04	18.82	0.694
Maximumesophageal dose	22.28	22.35	0.645

Values are given as Gy/CGE, unless otherwise noted.
* Statistically significant.

Andolino DL et Al. IJROBP, 2011



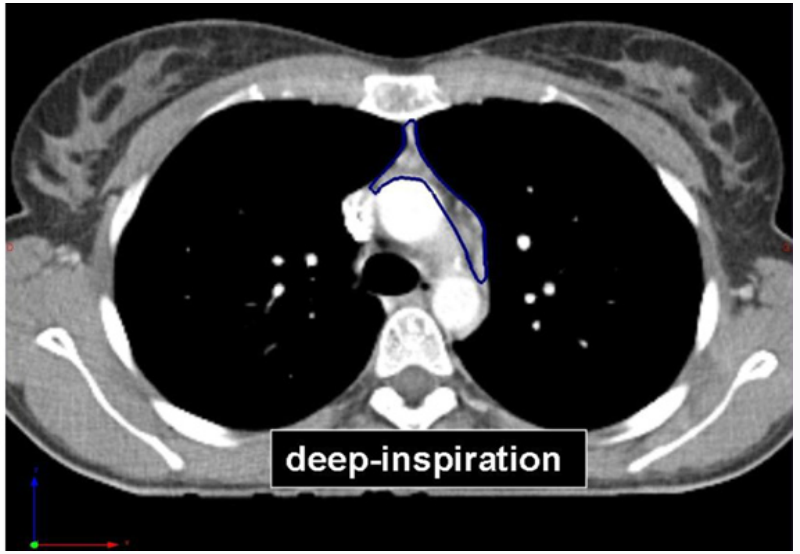


Table 2. Radiation dose to the different thoracic organs with free-breathing IMRT or deep-inspiration breath-hold IMRT, for all patients, the patients whose tumors were in the upper mediastinum, and those whose tumor involved more or less the whole mediastinum

Dosimetric parameter	Patient group	Free-breathing IMRT	Deep-inspiration breath-hold IMRT	Difference	*p* value
Mean coronary dose	All patients ($n = 28$)	18.2 (15.9–20.6)	15.2 (12.6–17.9)	16%	0.0002
	Upper mediastinum ($n = 11$)	13.9 (10.1–17.6)	8.8 (5.6–12.1)	37%	0.001
	Whole mediastinum ($n = 17$)	21.1 (18.7–23.4)	19.3 (17.2–21.6)	9%	0.002
Mean heart dose	All patients ($n = 28$)	8.4 (6.1–10.7)	7.1 (4.7–9.6)	15%	0.002
	Upper mediastinum ($n = 11$)	3.6 (2.5–4.7)	1.8 (1.4–2.2)	50%	0/001
	Whole mediastinum ($n = 17$)	11.5 (8.6–14.4)	10.6 (7.6–13.6)	8%	NS
Mean lung dose	All patients ($n = 28$)	11.8 (10.6–12.9)	9.4 (8.3–10.4)	20%	<0.0001
	Upper mediastinum ($n = 11$)	9.2 (8.4–10.1)	6.8 (6.3–7.3)	26%	0.001
	Whole mediastinum ($n = 17$)	13.4 (12–14.8)	11 (9.9–12.1)	18%	0.0003
Lung V20	All patients ($n = 28$)	21 (18–24)	15 (12–16)	28%	<0.0001
	Upper mediastinum ($n = 11$)	16 (13–19)	10 (8–12)	38%	0.001
	Whole mediastinum ($n = 17$)	24 (21–28)	17 (15–20)	29%	0.0003

Abbreviations: IMRT = intensity-modulated radiation therapy; NS = not significant.
Nonparametric *t* test for matched observations: Wilcoxon test: mean. 95% confidence interval in parentheses.

Paumier A et Al. IJROBP, 2011

RT evolution in HL

Dose 40 – 45 Gy >> 20 – 30 (36) Gy

Volume EF >> IF >> IN

Tecnica 2D >> 3D-CRT >> IMRT >> 3D-PT

Techniques evolution

Individualization (age, sex, comorbidities, site)

Suitable targets (target volume, shape)

OAR constraints

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0360-3016/10/$–see front matter

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doi:10.1016/j.ijrobp.2009.09.040

INTRODUCTORY PAPER

QUANTITATIVE ANALYSES OF NORMAL TISSUE EFFECTS IN THE CLINIC (QUANTEC): AN INTRODUCTION TO THE SCIENTIFIC ISSUES

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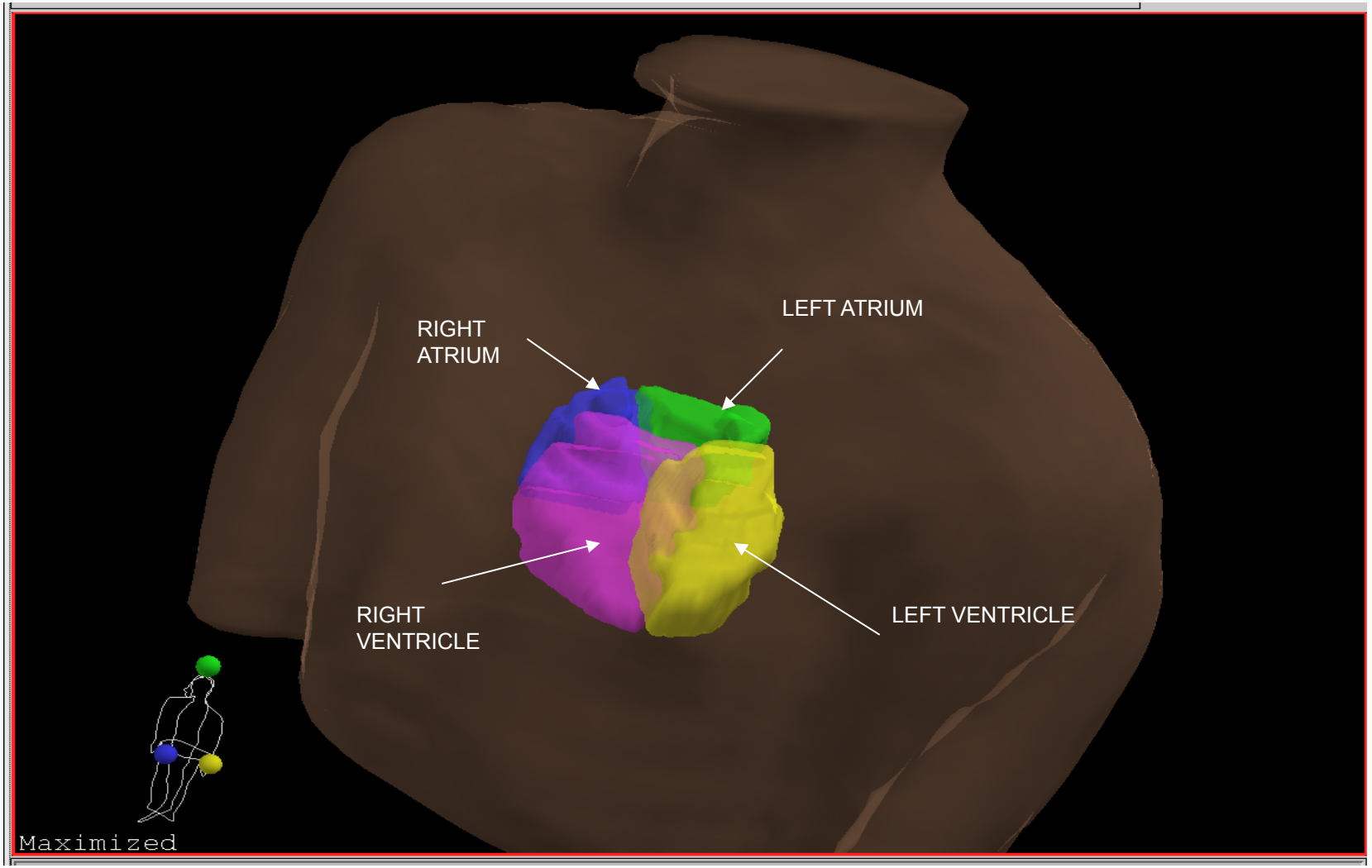
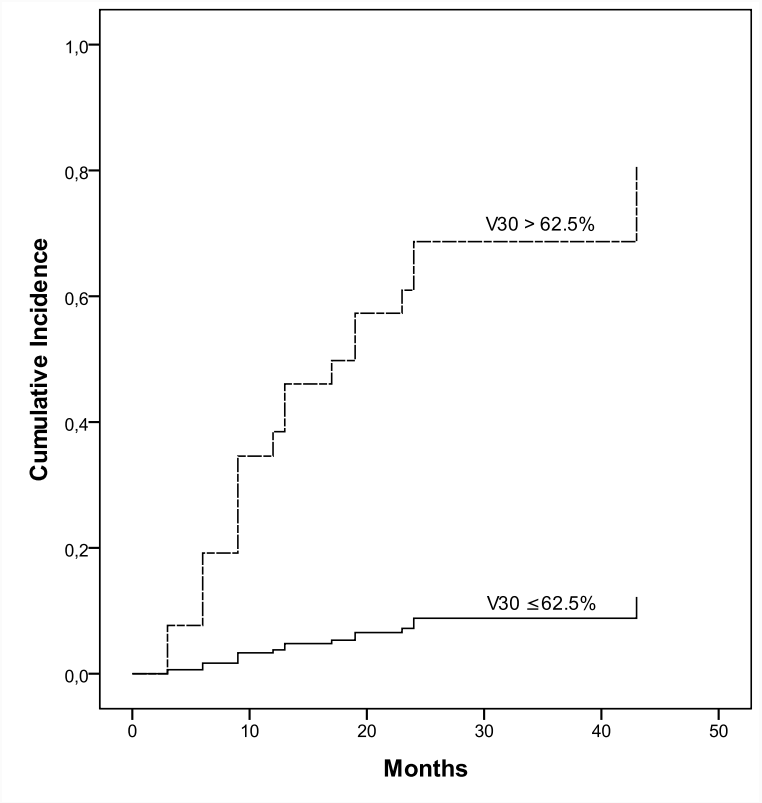
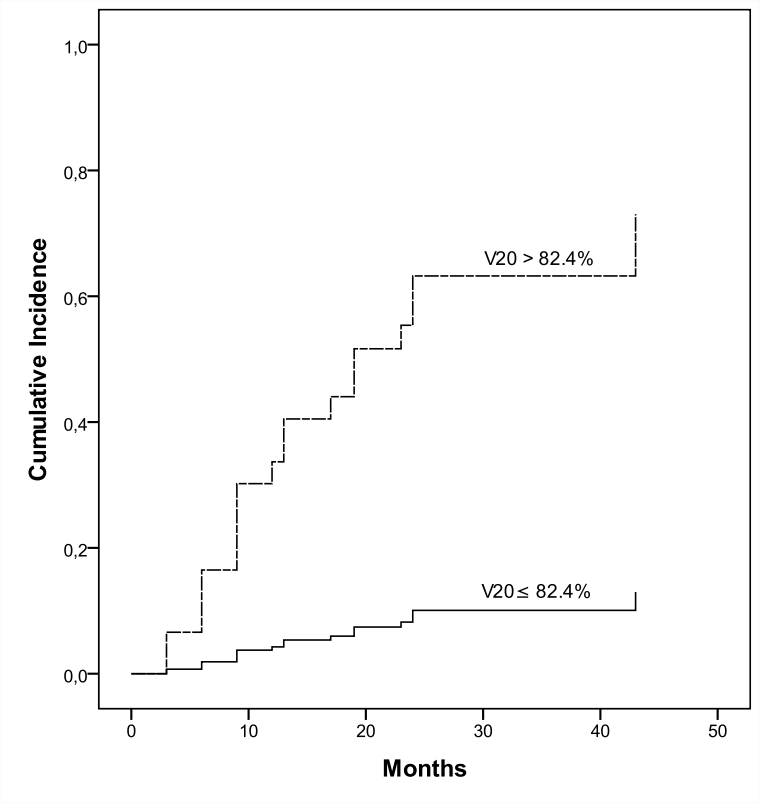
Advances in dose–volume/outcome (or normal tissue complication probability, NTCP) modeling since the seminal Emami paper from 1991 are reviewed. There has been some progress with an increasing number of studies on large patient samples with three-dimensional dosimetry. Nevertheless, NTCP models are not ideal. Issues related to the grading of side effects, selection of appropriate statistical methods, testing of internal and external model validity, and quantification of predictive power and statistical uncertainty, all limit the usefulness of much of the published literature. Synthesis (meta-analysis) of data from multiple studies is often impossible because of suboptimal primary analysis, insufficient reporting and variations in the models and predictors analyzed. Clinical limitations to the current knowledge base include the need for more data on the effect of patient-related cofactors, interactions between dose distribution and cytotoxic or molecular targeted agents, and the effect of dose fractions and overall treatment time in relation to nonuniform dose distributions. Research priorities for the next 5–10 years are proposed. © 2010 Elsevier Inc.



Cella L et Al. Radiother Oncol 2011



V30 tiroide



V20 tiroide

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Conclusions

✓Evolution in the indication, volume, dose and technical delivery of the radiation treatment in HL paves the way to a significant improvement of the late toxicity associated with older treament modalities.

✓Better knowledge of toxicity constraints coupled to an individualization of patients therapy technique will be necessary to fully utilize the available technology .