GRANDANGOLO

XXI CONGRESSO NAZIONALE AIRO

Genova, 19-22 novembre 2011
Porto Antico di Genova
Centro Congressi

Associazione Italiana Radioterapia Oncologica

V. DONATO

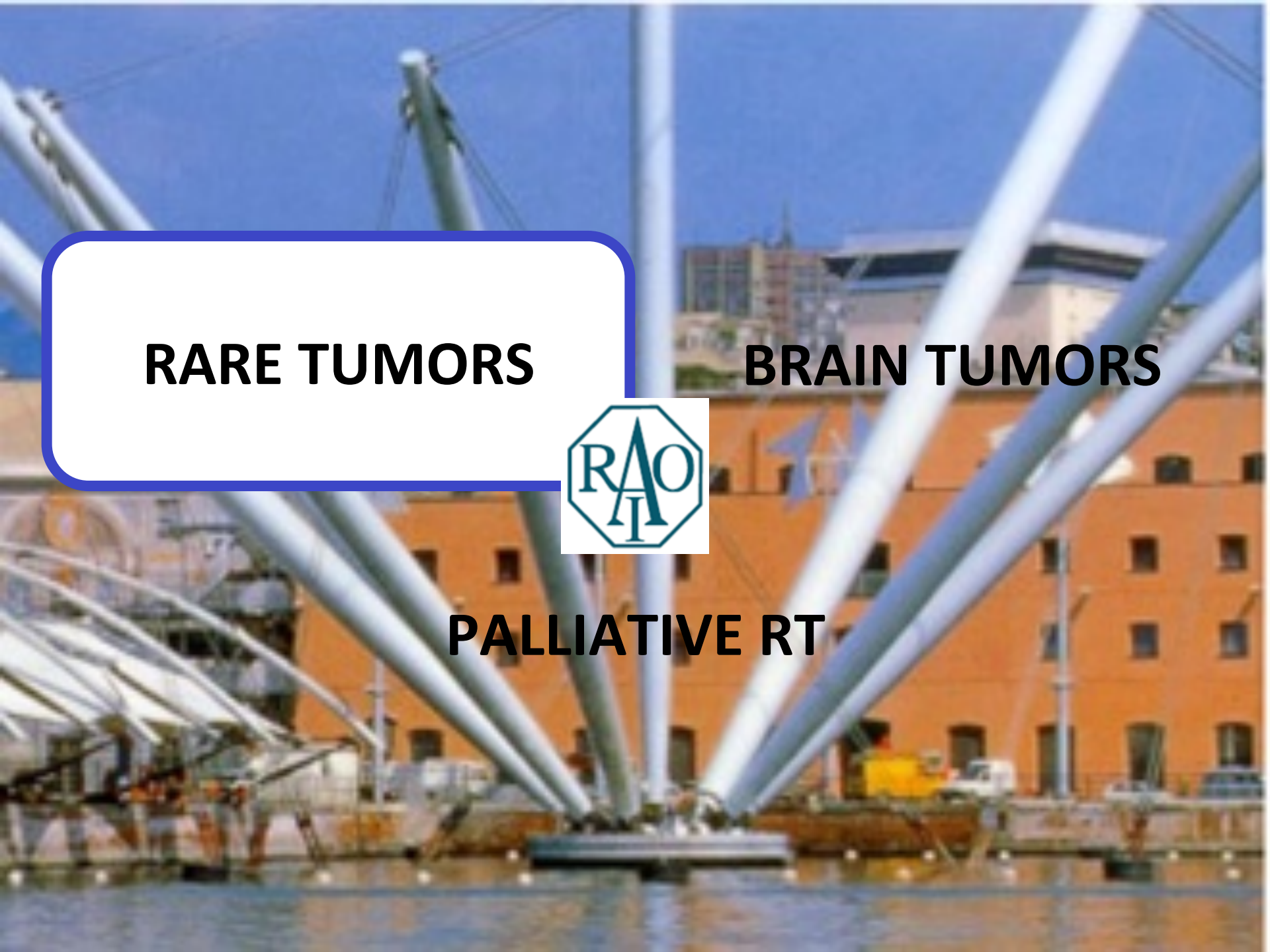
WORKING PROGRAM

NCCN National Comprehensive Cancer Network®

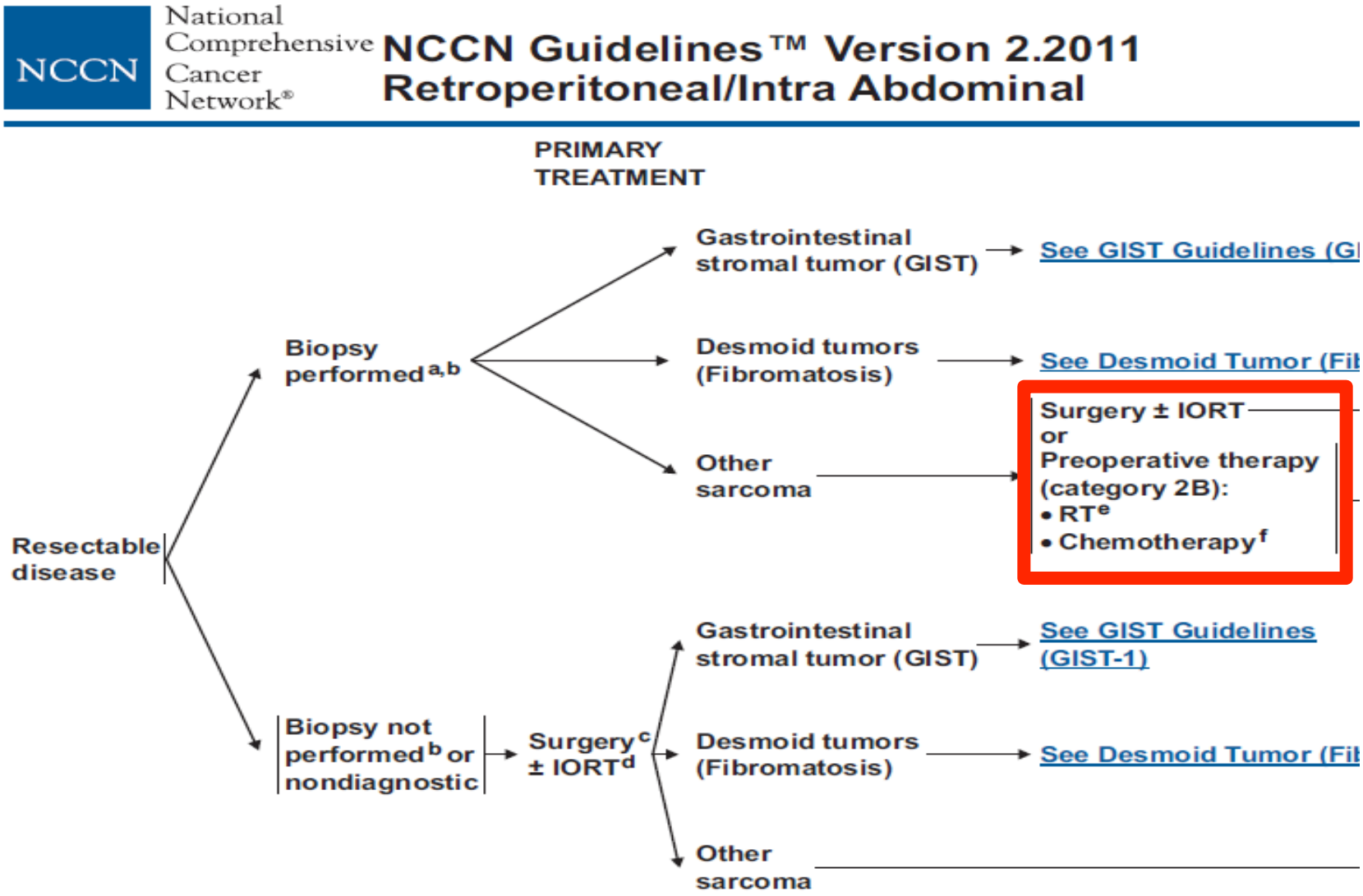
guideline

2011
International
articles

New Clinical Practice ?


RARE TUMORS
BRAIN TUMORS
RAO
PALLIATIVE RT

RARE TUMORS
RETROPERITONEAL SARCOMA
RATIONAL



Review Article

Radiotherapy and Surgery—An Indispensable Duo in the Treatment of Retroperitoneal Sarcoma

Lien Van De Voorde, MD[1]; Louke Delrue, MD[2]; Marc van Eijkeren, MD, PhD[1]; and Gert De Meerleer, MD, PhD[1]

MATERIALS AND METHODS

9 prospectively nonrandomized studies
10 retrospective studies

Table 1. Published Data on Patients Who Underwent *Surgery* as the Only Treatment Modality

Study			Results		
Author	No. of Patients	Follow-Up, mo	5-Year LRFS, %	5-Year DFS, %	5-Year OS, %
Neuhaus 2005[31]	58	26	NR	NR	45
Nishimura 2010[32]	82	24	35.4/10[a]	NR	62
Strauss 2010[33]	200	29	54.6	68.6	NR
Stoeckle 2001[18]	34[b]	47	23	NR	44

Table 2. Published Data on Patients Who Received *Postoperative Radiotherapy* as the Only Radiation Modality or in Combination With Other Radiation Modalities or Chemotherapy

Study		Postoperative EBRT								Results		
		Alone		With Preoperative EBRT		With IORT		With CT				
Author	No. of Patients	No.	Dose, Gy	No.	Dose, Gy	No.	Dose, Gy	No.	Follow-Up, mo	5-Year LC, %	5-Year DFS, %	5-Year OS, %
Stoeckle 2001[18]	145	89	50	None	–	None	–	ND[a]	47	52	29	49
Lewis 1998[16]	231	66	ND	ND	–	ND	–	172	28	59	NR	54
Gilbeau 2002[43]	45	28	49	None	–	14[b]	15	11	53	40	NR	60
Zlotecki 2005[13]	40	25	50	None[c]	–	None	–	ND[d]	34	65	NR	69 vs 12[e]

Cancer 2011 117:4355–64.

Table 3. Published Data on Patients Who Received *Intraoperative Radiotherapy* as the Only Radiation Modality or in Combination With Other Radiation Modalities or Chemotherapy

		IORT										
Study		Alone		With EBRT		With Postoperative BT		With CT		Results		
Author	No. of Patients	No.	Dose, Gy	No.	EBRT/IORT Dose, Gy	No.	Dose, Gy	No.	Follow-Up, mo	5-Year LC, %	5-Year DFS, %	5-Year OS, %
Petersen 2002[17]	87	10	15[a]	77[b]	47.6/15	None	—	10	42	59	29	48
Gieschen 2001[45]	37	None	—	20	45/10-20	None	—	None	38	59	38	50
Alektiar 2000[10]	32	7	12-15	25	50.4/12-15	2	140-160	4	33	62	55	45
Bobin 2003[46]	24	None	—	22[c]	45-50/15	None	—	5	53	NR	28	56
Ballo 2007[47]	83	None	—	18[d]	50-55/15	None	—	ND[e]	47	40 (at 10 y)	39 (at 10 y)	NR
Krempien 2006[48]	67	22	15	45	45/15	None	—	None	30	40	28	64
Pierie 2006[49]	103	None	—	14[f]	10-20	None	—	ND[g]	27	NR	NR	48
Dziewirski 2010[50,51]	57	22	20	34	50	None	—	None	40	65	NR	50

Table 4. Published Data on Patients Who Received *Preoperative Radiotherapy* as the Only Radiation Modality or in Combination With Other Radiation Modalities or Chemotherapy

		Treatment										
Study		Preop EBRT Alone		Preop EBRTand Postop BT		Preop EBRT and IORT		Postop EBRT and CT		Results		
Author	No. of Patients	No	Dose, Gy	No.	Dose, Gy	No.	Dose, Gy	No.	Follow-Up, mo	5-Year LC, %	5-Year DFS, %	5-Year OS, %
Pisters 2007[12]	35	13	50.4	0	—	22	15	35	NR	NR	NR	NR
Jones 2002[44]	46	21	45	19[a]	25	0	—	0	19	NR	80 (at 2 years)	NR
Tzeng 2006[19]	16	16	57.5	0	—	0	—	0	28	80 (at 2 years)	NR	NR
White 2007[55]	38	25[b]	46.5	0	—	0	—	0	57	NR	80 (primary)	74 (90% primary)
Gieschen 2001[45]	37	17	45	0	—	20	10-20	None	38	59	38	50

Preop indicates preoperative; EBRT, external-beam radiotherapy; Postop, postoperative; BT, brachytherapy; IO apy; Gy, grays; LC, locoregional control; DFS, disease-free survival, OS, overall survival; NR, not reported.

[a] Nineteen patients received preoperative EBRT plus BT, 2 patients received BT alone, and 2 patients received BT and postoperative EBRT.

[b] Eleven patients received palliative RT versus 25 patients who received EBRT and underwent surgery.

Cancer 2011 117: 4355–64.

RESULTS

Surgery

LR is the major cause of
mortality and continues to occur after 5 years of follow-up.

RT

•The use of RT is low often omitted from treatment schedules because of a lack of level I evidence.

•The addition of IORT sometimes produces promising disease control rates, although high toxicity rates have been reported, with peripheral neuropathy the most frequent and severe.

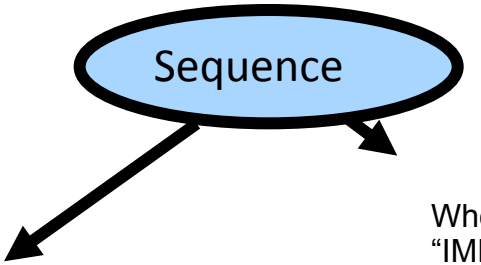
•IMRT, tomotherapy, and intensity-modulated arc therapy technologies of choice are less toxic.

Cancer 2011 117: 4355–64

DISCUSSION

Author's Recommendation

Neo-adjuvant EBRT +/- IORT to surgery improves LCR and may be associated with improved OS



When preferred Postoperative RT
"IMRT and arc therapy technology are used preferentially treshold dose of 55 Gy"

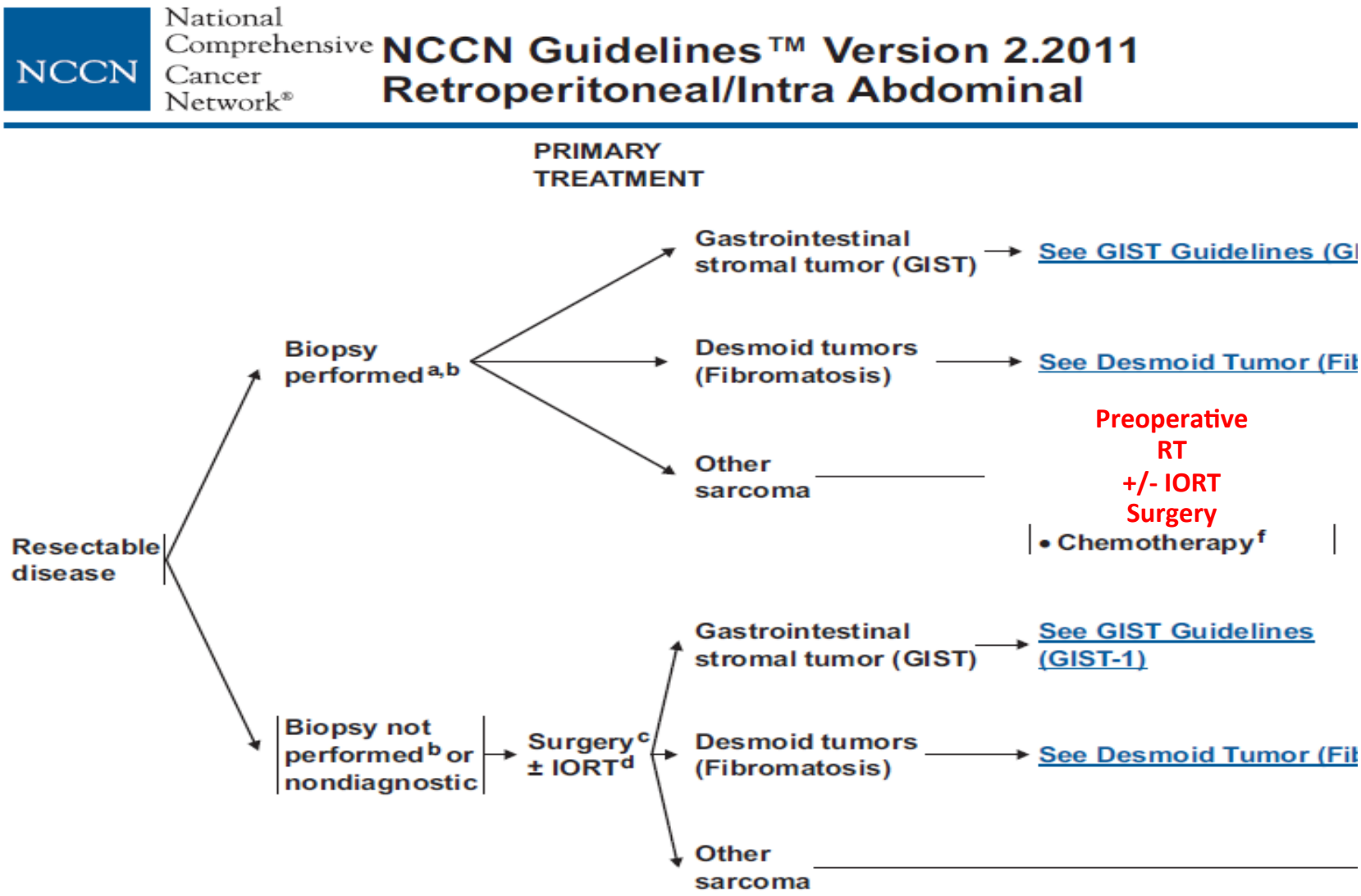
Preoperative EBRT
low gastrointestinal toxicity

Although surgeons still are the gatekeepers of treatment, RSTS should be discussed and treated in a multidisciplinary setting.

"The presence of a radiation oncologist is vital. "

Cancer 2011 117: 4355–64

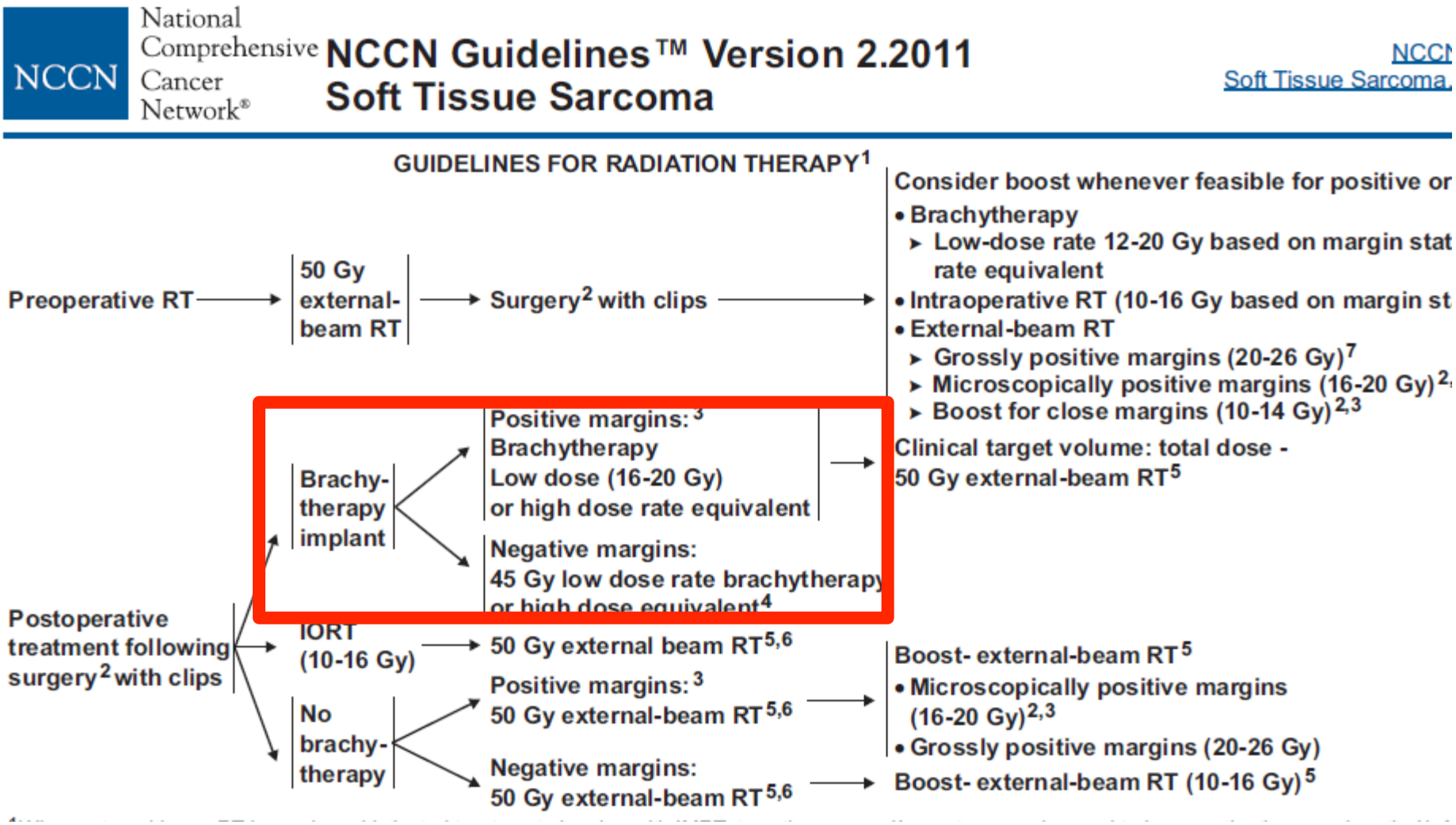
RARE TUMORS
RETROPERITONEAL SARCOMA
FUTURE GUIDELINE



THERAPEUTIC APPROPRIATENESS
HIGH GRADE SARCOMA OF THE EXTREMITY

LC COMPARISON ADJUVANT BRT VS IMRT

RATIONAL



MATERIALS AND METHODS

134 pts treated from 1995 to 2006

After Limb sparing surgery:

- LD BRT 71 pts (53%) median dose 45 Gy
- IMRT 63 pts (47%) median dose 53 Gy

Follow up 46 months

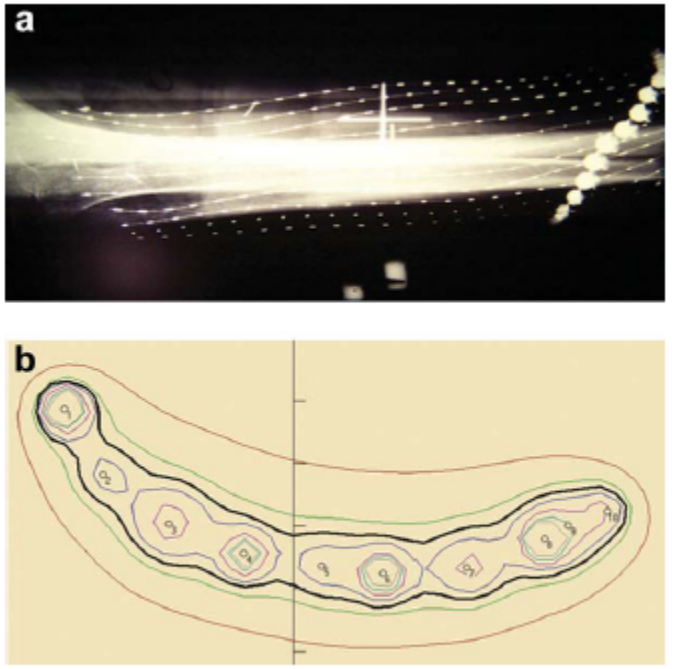


Figure 1. Brachytherapy. (a) Plain X-ray film demonstrating afterloading catheters. (b) Axial dose rate distribution. Solid line represents prescription isodose rate line.

Kaled M. Alektiar, MD
Memorial Sloan-Kettering Cancer Center, NY,
Cancer July 15, 3229-3234 2011

RESULTS

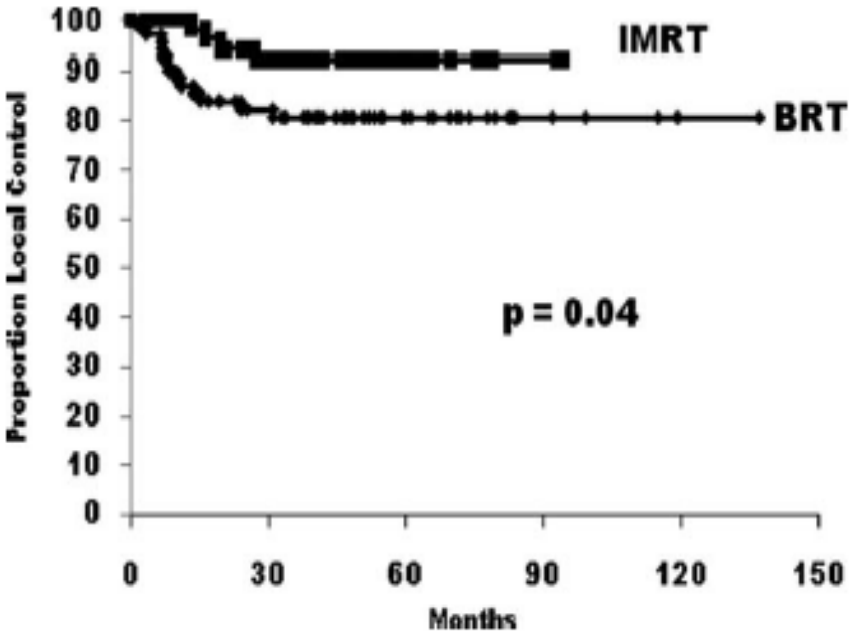


Figure 3. Local control and radiotherapy (RT) type. IMRT indicates intensity-modulated RT; BRT, brachytherapy.

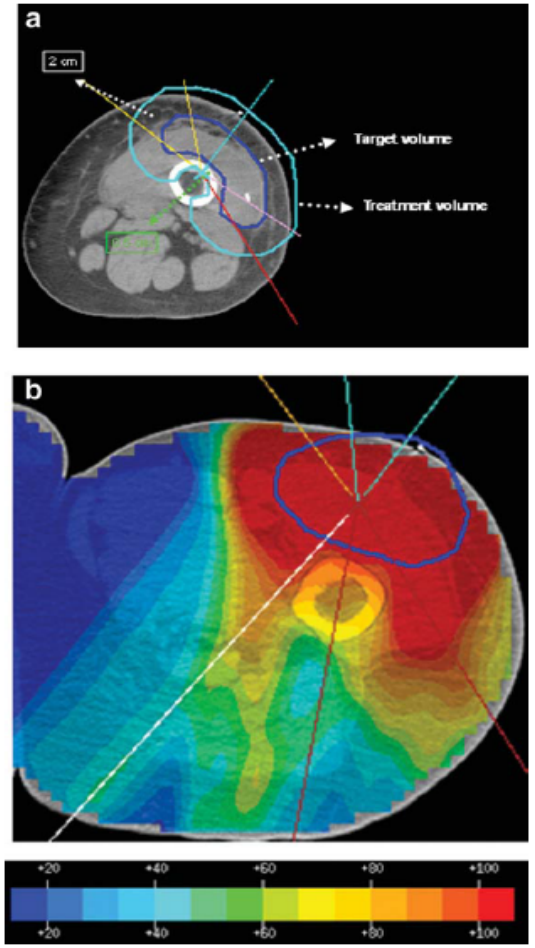


Figure 2. Intensity-modulated radiotherapy (IMRT). (a) Axial margin expansion in soft tissue compared to that with bone interface. (b) IMRT dose distribution.

DISCUSSION

5-year LC

IMRT 92% BRT 81% (P= 0.04).

Difference between the 2 groups. IMRT group has

1) High proportion of patients with locally advanced disease.

2) More patients with tumors >10 cm (52% vs 30%, P = 0.005)

3) More patients requiring manipulation (stripping/resection) of bone

(30% vs 13%, P = 0.02) and nerve (54% vs 14%, P =0.002)

4) More patients with positive/close (<1mm) margins (49% vs 20%, P =0.006)

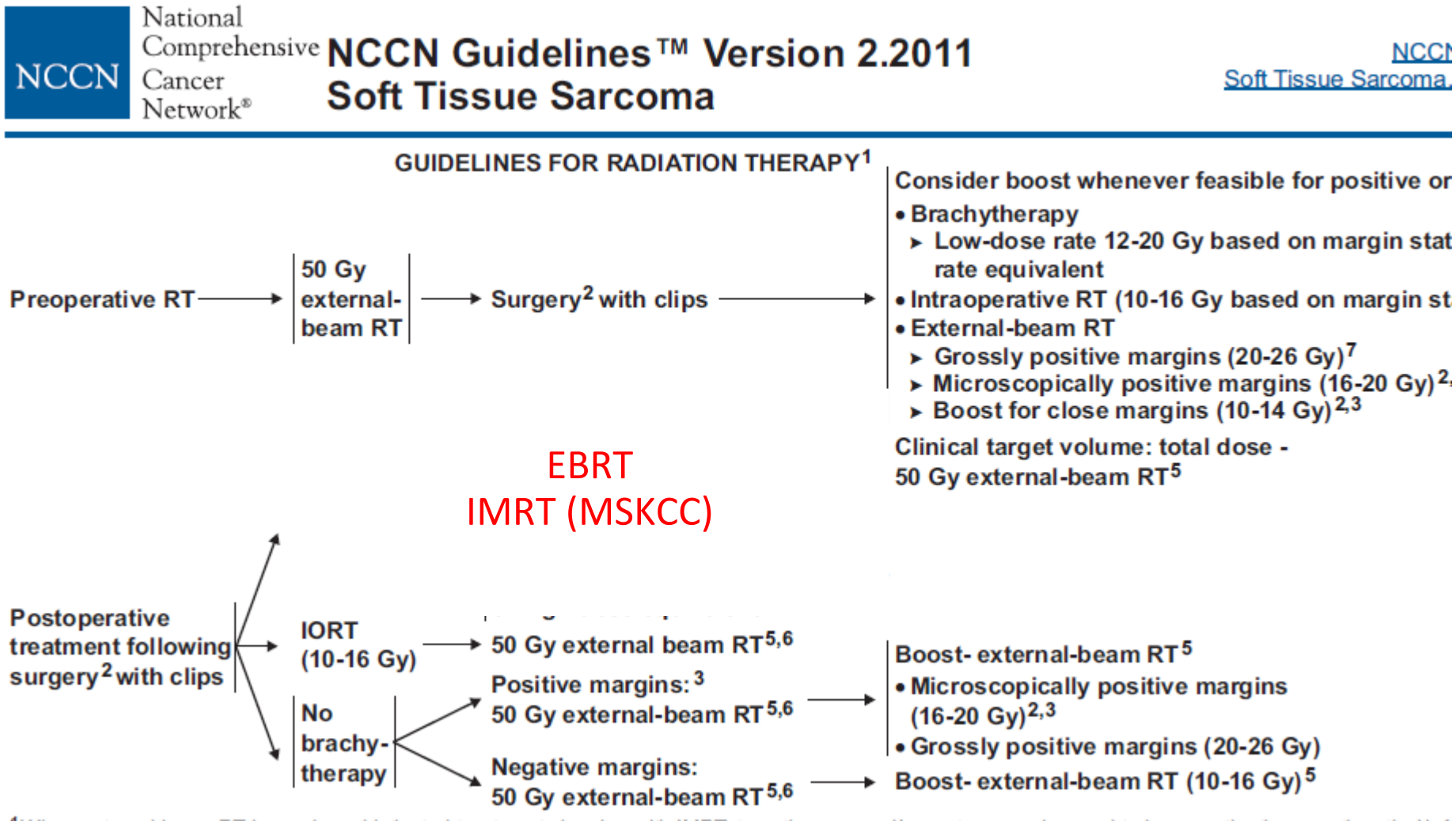
Despite adverse features in the IMRT group, LC was

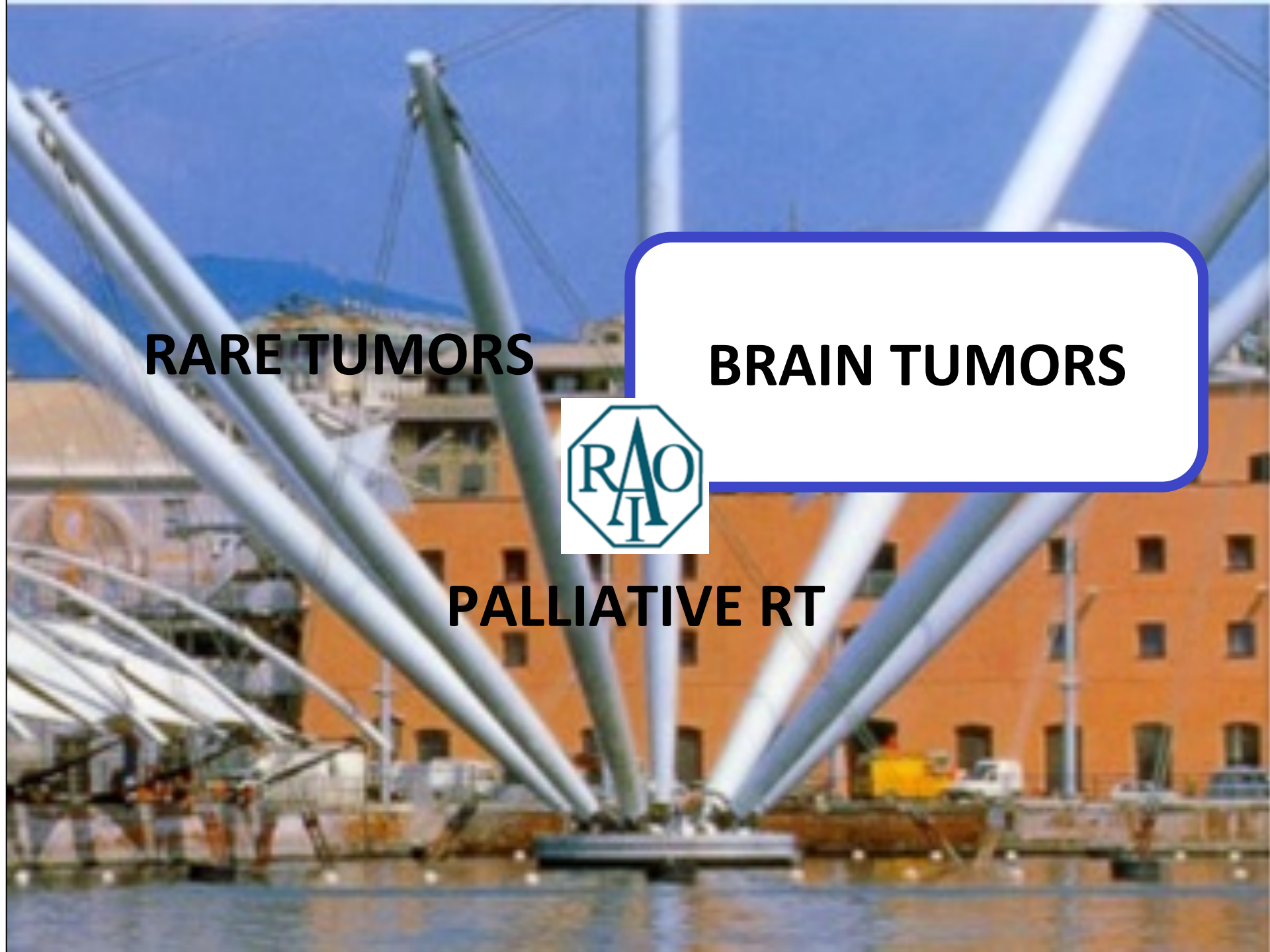
significantly better than BRT on univariate as well as multivariate analysis

Althoug this is not a randomised trial, IMRT is currently the preferred method of delivering adjuvant RT at MSKCC based on the high rate of local control achieved

THERAPEUTIC APPROPRIATENESS
HIGH GRADE SARCOMA OF THE EXTREMITY
LC COMPARISON ADJUVANT BRT VS IMRT

BASED ON MEMORIAL SLOAN-KETTERING CANCER CENTER




RARE TUMORS
BRAIN TUMORS
RAO
PALLIATIVE RT

NEW PERSPECTIVES IN HIGH GRADE GLIOMAS

ASTRO ANNUAL MEETING
SCIENCE BASED, PATIENT DRIVEN
53rd ANNUAL MEETING | OCTOBER 2-6, 2011 | MIAMI BEACH CONVENTION CENTER | MIAMI BEACH, FLA.

1049 **A Phase II Study of Surgical Excision, Temozolomide, Radiotherapy, and Anti-EGFR Radioimmunotherapy (EXTRA) as Adjuvant Therapy in High-grade Gliomas**

L. C. Daugherty[1], S. Morales[1], b. fisher[1], L. Li[2], J. Kim[3], T. Quang[4], J. Emrich[1], T. Yaeger[5], L. Komarnicky[1], L. W. Brady[1]

[1]Hahnemann University Hospital, Philadelphia, PA, [2]Fox Chase Cancer Center, Philadelphia, PA, [3]City of Hope, Duarte, CA, [4]University of Washington, Seattle, WA, [5]Wake Forest University, Winston Salem, NC

MATERIALS AND METHODS

390 pts treated from 1988 to 2007 with new diagnosed GBM or AA
1) CTL: Surgery+RT (60 Gy)
2) RIT: Surgery+RT +125I-EGFR Mab 425
3) RIT+TMZ : Surgery+RT+TMZ+125I-EGFR Mab 425

RESULTS

Median survival
1) CTL: 7.3 months
2) RIT: 39.7 months
3) RIT+TMZ :79.4 months

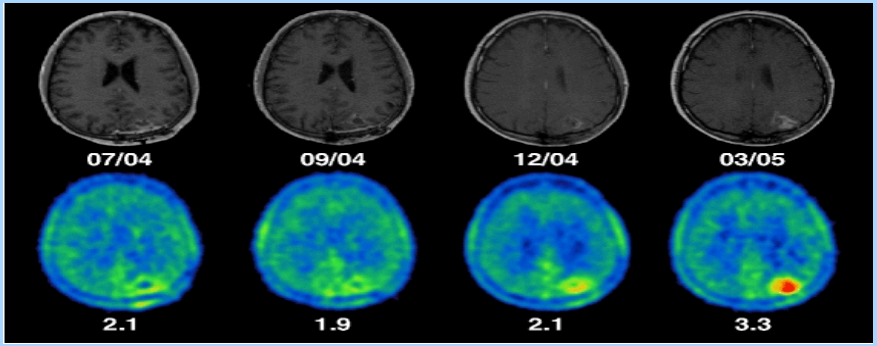
IJROBP Vol 81 Num 2 Suppl 2011

RATIONALE

EGFR is highly expressed in up to 60–90% in high-grade gliomas

425 anti-EGFR antibody (mAb 425)
IgG2a developed from mice immunized

PET CT with 111 indium-labeled mAb 425 shows :
90% sensitivity,
60% specificity,
90% accuracy to gliomas.



direct cell growth inhibition
complement-dependent
cytotoxicity
activation of the humoral respons

mAb 425

radioactive
125I

radiation-mediated DNA damage.

Synergistic
Anticancerogenic
effect

J Neurosurg 113 LINNA LI et all:192–198, 2010

CONCLUSION

Adjuvant 125I-EGFR Mab 425 radioimmunotherapy with or without TMZ should be considered in the menagment of AA and GBM

Luther W. Brady

OUR QUESTION

Based on the results of the study shown at ASTRO 2011, how is it possible that this strategy (surgery+RT+TMZ+125I-EGFR MAb 425 or surgery+RT+125I-EGFR MAb 425) is not accepted as gold standard treatment yet?

HIS ANSWER

It is a shame that there has been so much difficulty actually in having it brought to market as a commercial product. Without question, it is a significant and major improvement in treatment of high grade gliomas of the brain as demonstrated by the data presented by Dr. Daugherty in Miami. However, the machinations that go on with regard to taking a product to commercial production is complicated and difficult.

BRAIN TUMORS
OBSERVATION VS RT FOR ADULT PILOCYTIC ASTROCYTOMA
RATIONAL

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 2.2011
Central Nervous System Cancers

Seizure is a common symptom (81%) of low-grade gliomas, and is more frequently associated with oligodendrogliomas.[7] The median duration from onset of symptoms to diagnosis ranges from 6 to 17 months. These tumors typically are non-enhancing, low-attenuation lesions on CT scans and MRI scans.

Diffuse astrocytomas are poorly circumscribed, invasive, and gradually evolve into higher-grade astrocytomas. Although these were traditionally considered benign, they can behave aggressively and will undergo anaplastic transformation within 5 years in approximately half of patients.[8, 9] The most common non-infiltrative astrocytomas are pilocytic astrocytomas, which are circumscribed, often surgically resectable, and rarely transform; however, the NCCN algorithm does not encompass pilocytic astrocytomas because these tumors are curable by surgery alone.

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Biopsy results can
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The role of maxima
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Original Article

Upfront Observation Versus Radiation for Adult Pilocytic Astrocytoma

Adrian Ishkanian, MSc, MD[1]; Normand J. Laperriere, MD[1]; Wei Xu, PhD[2]; Barbara-Ann Millar, MD[1]; David Payne, MD[1]; Warren Mason, MD[3]; and Arjun Sahgal, MD[1,4]

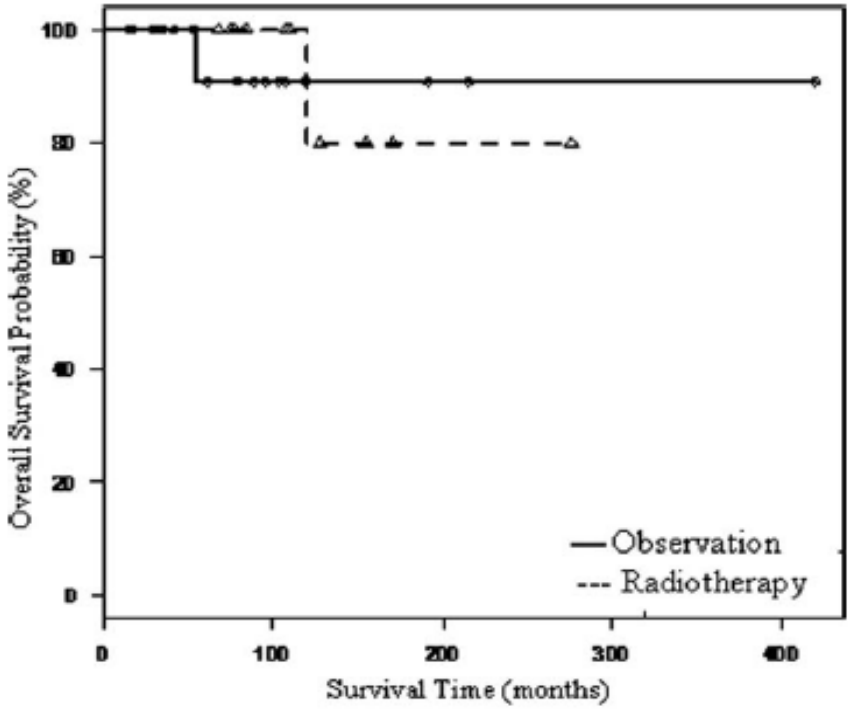
MATERIALS AND METHOD

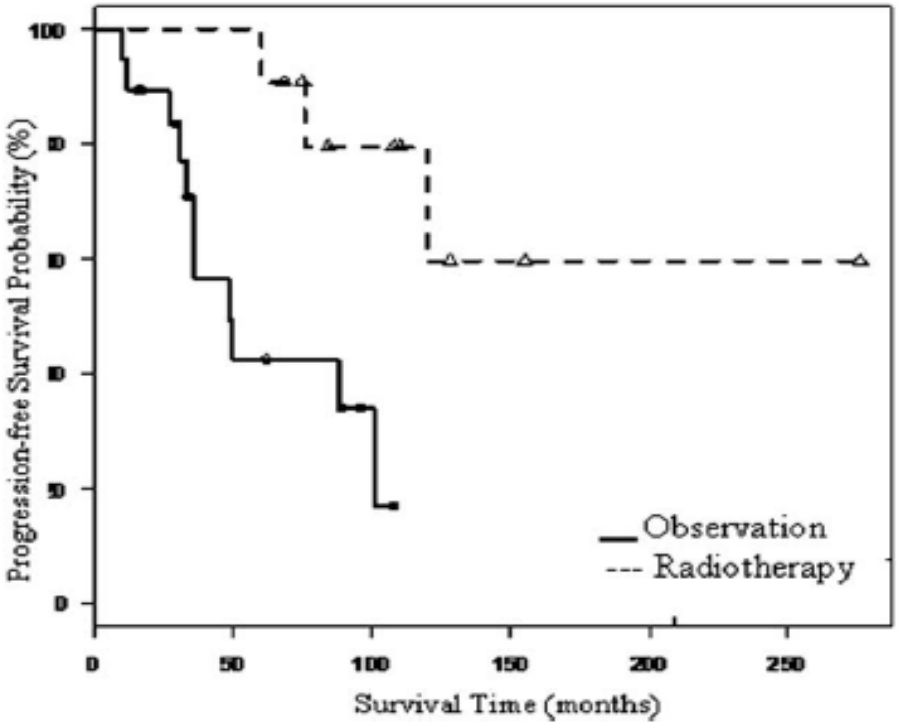
From 1971 to 2007
30 adults retrospectively reviewed
median age 30 years (18-64)
19/30 (63%) Observation post surgery
Surgery: Biopsy, STR (subtotal resection),GTR (gross total resection)
11/30 (37%) Adjuvant RT
Radiation given within 6 months of the operation
5000 cGy/25 fractions
Median follow-up 87 months (16-420)

Princess Margaret Hospital, Toronto, ON, Canada

Cancer 2011;117:4070–9.

RESULTS





5-year OS
Observation 91% RT 100%

10-year OS
Obervation 91% RT 80%

(P = 0 .94)

5-year PFS
Observation 42% RT 91%

10-year PFS
Observation 17% RT 60%.

(P = 0 .005)

BRAIN TUMORS
OBSERVATION VS RT FOR ADULT PILOCYTIC ASTROCYTOMA
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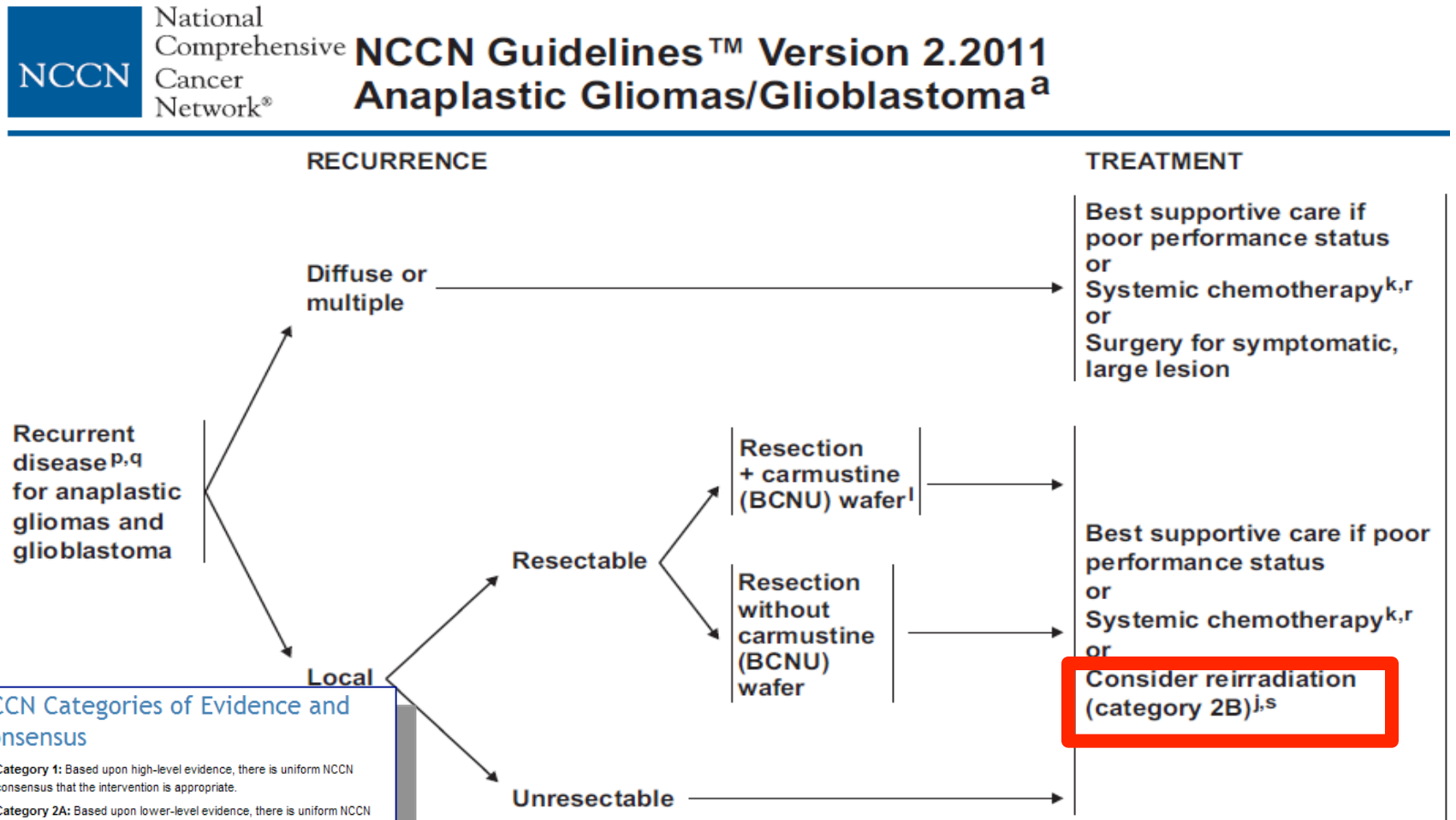
thus, small sample

The role of maxima
unresolved. Becau
series generally inc
additional variables
excision was based
approach is relative
modern postoperat
received RT, and th

In pilocytic astrocytomas adjuvant RT is raccomended (improve DFS) and mandatory for tumors located in eloquent areas of the brain in which progression may render significant neurologic deficits.

RECURRENT GLIOBLASTOMA
RATIONALE

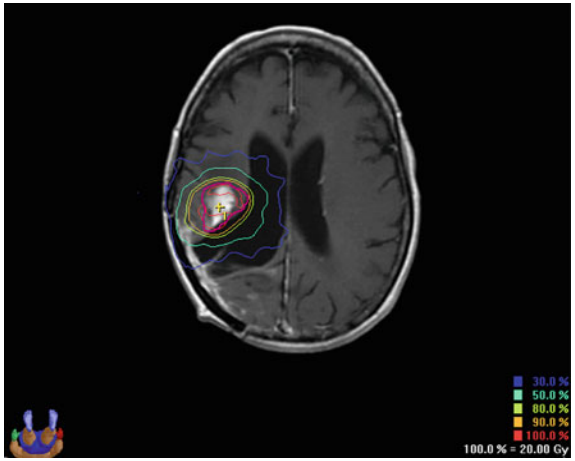


STEREOTACTIC SRS

(Leksell Gamma Knife, adapted linear accelerators, Cyber Knife ecc)

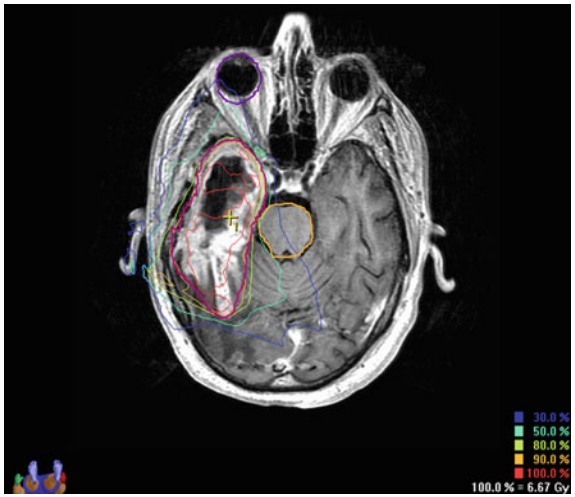
smaller volumes

usually given in a single fraction.



FRACTIONATED STEREOTACTIC RT

dose divided over several fractions.
used to treat larger volumes



Limiting the target volume to approximately 4-5 cm minimises the risk of toxicity
suggest that if larger volumes are being targeted consideration should be made to reducing the dose.

C. Nieder, J.A.Langendijk
Re-Irradiation : New Frontiers
2011

2122 Generation and Validation of a Prognostic Score to Predict Outcome after Re-irradiation of Recurrent Glioma

S. Combs, T. Welzel, S. Rieken, W. Wick, J. Debus

Universitätsklinikum Heidelberg, Heidelberg, Germany

ASTRO ANNUAL MEETING
SCIENCE BASED, PATIENT DRIVEN
53rd ANNUAL MEETING | OCTOBER 2-6, 2011 | MIAMI BEACH CONVENTION CENTER | MIAMI BEACH, FLA.

MATERIALS AND METHODS

233 pts: GBM 89 (38%),
Grade III WHO 52 (22%),
LGG 92 (40%)

Reirradiation : Fractionated Stereotactic RT (FSRT),med Dose 36 Gy (2 Gr/fr)

IJROBP Vol 81 Num 2
Suppl 2011

RESULTS

Median Survival : GBM 8 months,
Grade III WHO 20 months,
LGG 24 months

Three strongest Prognostic Factor:

1) **Histology** ($p<0.0001$)
2) **Age <50 yrs vs ≥50 yrs** ($p<0.0001$)
3) **Time between first and re-irradiation ≤12 vs >12 months** ($p=0.00051$)

4) Tumor volume at re-irradiation
5) Karnofsky Performance Score

DISCUSSION

PROGNOSTIC SCORE
Additive scale (range 0-4 points)

Survival after re-irradiation ($p<0.0001$)
Excellent (0 points)- 25 months
Good(1 points)-22 months
Moderate (2 points)-13 months
Poor (4 points)-8/9 months

Example:

Group 0 (median survival 25 months)

- LGG histology,
- time for re-irradiation > 12 months
- Age < 50 yrs

IJROBP Vol 81 Num 2 Suppl 2011

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 3, pp. 835–841, 2011

0360-3016/$–see front matter

doi:10.1016/j.ijrobp.2009.11.058

CLINICAL INVESTIGATION **Brain**

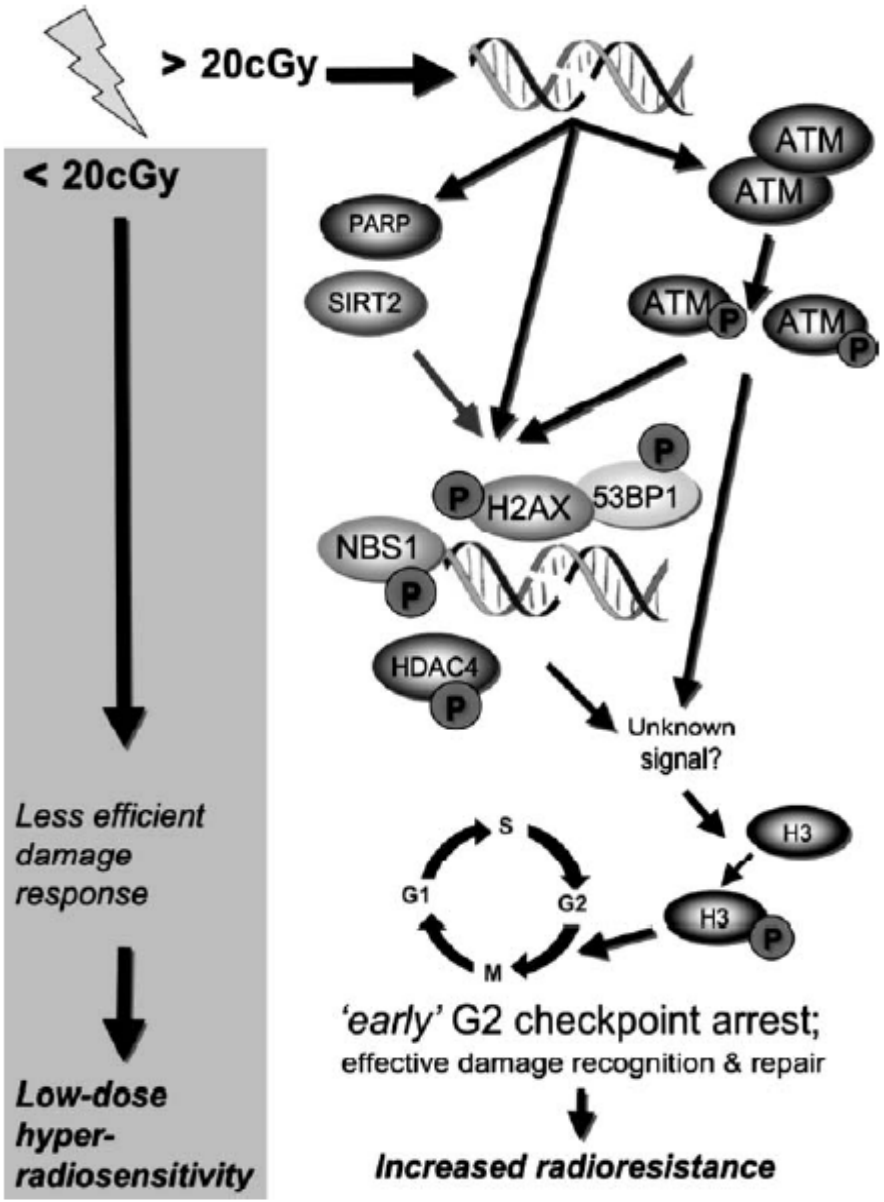
REIRRADIATION OF LARGE-VOLUME RECURRENT GLIOMA WITH PULSED REDUCED-DOSE-RATE RADIOTHERAPY

JARROD B. ADKISON, M.D.,* WOLFGANG TOMÉ, PH.D.,*† SONGWON SEO, M.S.,‡
GREGORY M. RICHARDS, M.D.,* H. IAN ROBINS, M.D., PH.D.,* KARL RASSMUSSEN, B.S.,†
JAMES S. WELSH, M.S., M.D.,* PETER A. MAHLER, M.D., PH.D.,* AND STEVEN P. HOWARD, M.D., PH.D.*

Departments of *Human Oncology, †Medical Physics, and ‡Biostatistics, University of Wisconsin School of Medicine and Public Health, Madison, WI

MATERIALS AND METHODS

December 2000 - September 2007
103 recurrent primary brain tumors
Definitive RT 59,4 Gy (range 50,4 -72,5 Gy)
Median PRDR 50 Gy (range 22-58 Gy)
Pulse of 0,2 Gy (intervals 3 min) apparent dose rate of 0.0667 Gy/min
Mean treatment volume 396.2 cm³ (range 89.6 -1002.2)
PTV : 2 cm-expansion sorrounding T2-weighted MRI edema



RATIONALE

LOW DOSE HYPERSENSITIVITY

- A damage threshold must be exceeded to active repair
- Low dose radiation damage lets G2 cells enter mitosis prematurely
- Damage persists undetected for many days after RT

B. Marples
Cancer and metastases reviews 23:197-207; 2004

RESULTS

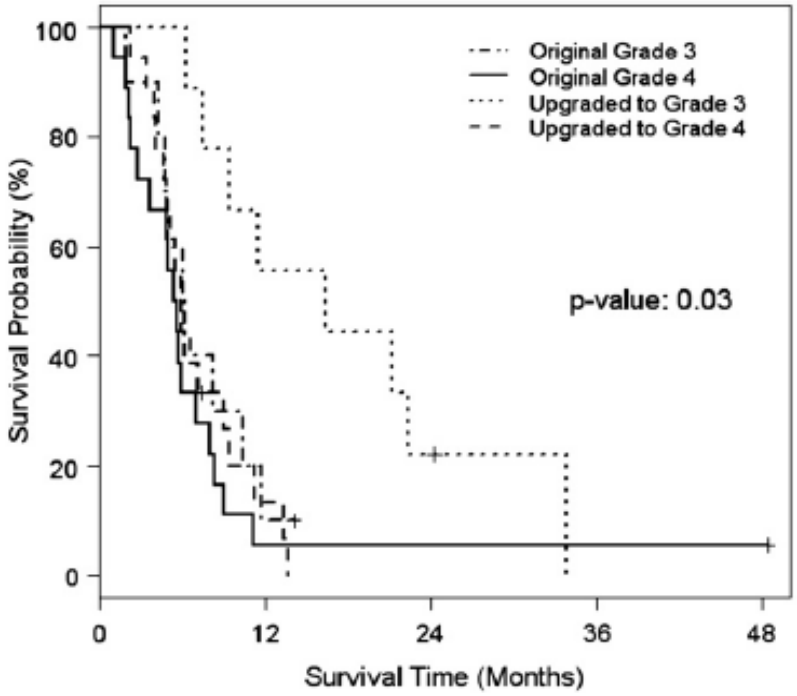


Fig. 3. Survival from initiation of pulsed reduced-dose-rate radiotherapy for patients who had undergone repeat tissue diagnosis before pulsed reduced-dose-rate radiotherapy.

OS from the initiation PRDR
Grade I-II 11.4 months (range 1-33.8)
Grade III 5.6 months (range 1.2-23.7)
Grade IV 5.1 months (range 1-48.8)

Table 3. Multivariate model for overall survival from initial diagnosis

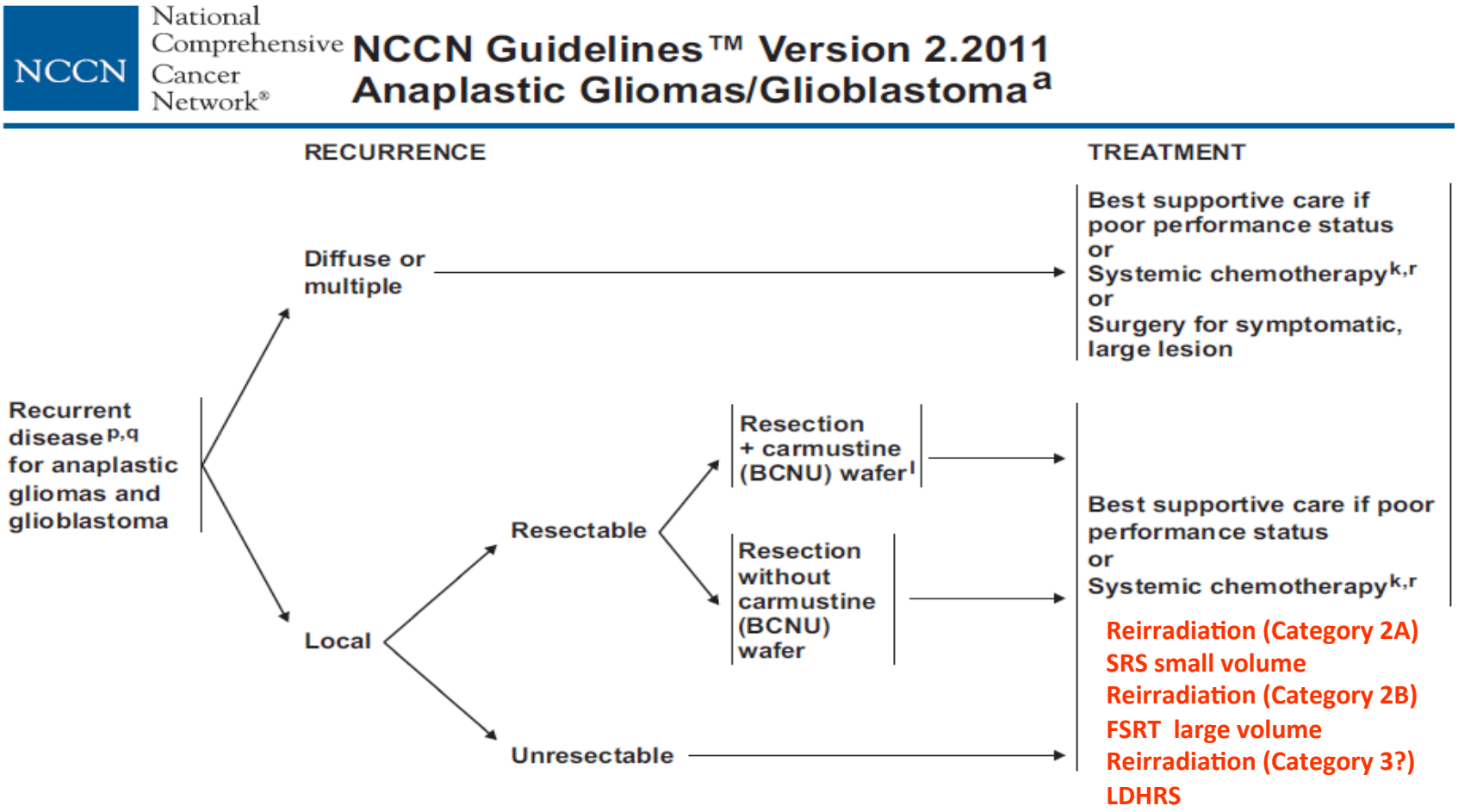
Variable	HR	95% CI for HR	*p*	Global *p*
Histologic grade at initial diagnosis				<.0001
Grade 3 ($n = 34$; vs. Grade 1-2, $n = 23$)	2.42	1.23–4.78	.01	
Grade 4 ($n = 46$; vs. Grade 1-2, $n = 23$)	7.74	3.70–16.17	<.0001	
Age at initial diagnosis (≥50 y, $n = 34$; vs. <50 y, $n = 69$)	2.70	1.66–4.41	<.0001	
Secondary surgery (none/biopsy, $n = 50$; vs. subtotal/gross, $n = 53$)	2.02	1.32–3.10	.001	

Abbreviations: HR = hazard ratio; CI = confidence interval.

Table 4. Multivariate model for survival from initiation of PRDR

Variable	HR	95% CI for HR	*p*
Histologic grade at initial diagnosis (Grade 3-4, $n = 80$; vs. Grade 1-2, $n = 23$)	1.74	1.01–3.00	.04
Age at initial diagnosis (≥50 y, $n = 34$; vs. <50 y, $n = 69$)	2.11	1.33–3.34	.002
Karnofsky performance status (<80, $n = 36$; vs. ≥80, $n = 67$)	1.72	1.13–2.62	.01

RECURRENT GLIOBLASTOMA
RATIONALE




RARE TUMORS
BRAIN TUMORS
RAO
PALLIATIVE RT

ECCO 16 ESMO 36 ESTRO 30
The European Multidisciplinary Cancer Congress
Integrating basic & translational science, surgery, radiotherapy, medical oncology, a
STOCKHOLM, 23-27 SEPTEMBER 2011

Presidential Session II
Sunday 25 September 2011, 12:20-14:40
7LBA LATE BREAKING ABSTRACT

A Multicentre Randomised Trial of Ibandronate Compared to Single Dose Radiotherapy for Localised Metastatic Bone Pain in Prostate Cancer (RIB)

P. Hoskin[1], S. Sundar[2], K. Reczkos[3], S. Forsyth[3], N. Mithal[4], B. Sizers,

First large Randomised Phase III trial bisphosphonate drug single dose

vs

single dose radiotherapy

Randomised 470 pts with primary prostate cancer and painful bone metastases

Pain relief (WHO pain ladder / Mercadante method - analgesic use)

WHO response rate from 70% (RT) to 85% (IB).

Mercadante method

4 weeks : more patients IB group worse Mercadante scores needed retreatment

6 and 12 months : no long-term difference

Median survival

11.8 months (radiotherapy only),
11.4 months (IB only),
12.7 months (radiotherapy then IB),
16.8 months (IB then radiotherapy)


ARTICLE IN PRESS

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0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.02.008

CLINICAL INVESTIGATION

UPDATE OF THE INTERNATIONAL CONSENSUS ON PALLIATIVE RADIOTHERAPY ENDPOINTS FOR FUTURE CLINICAL TRIALS IN BONE METASTASES

EDWARD CHOW, M.B.B.S.,* PETER HOSKIN, M.D.,† GUNITA MITERA, PH.D.(C),* LIANG ZENG, B.SC.(C),* STEPHEN LUTZ, M.D.,‡ DANIEL ROOS, M.D.,§ CAROL HAHN, M.D.,‖ YVETTE VAN DER LINDEN, M.D.,¶ WILLIAM HARTSELL, M.D.,# AND ESHWAR KUMAR, M.B.B.S. ** ON BEHALF OF THE INTERNATIONAL BONE METASTASES CONSENSUS WORKING PARTY

CONCLUSION

'IB was as good as single

OUR QUESTION

Is it possible to replace RT with bisphosphonate drug for those patients who nowadays must be treated, for every single anatomical place, with the former ?

Hoskin

HIS ANSWER

I think it does mean that in prostate cancer both options are reasonable choices and that if one doesn't work the alternate may well do so. I am not sure it replaces but rather compliments RT and gives us another option especially for the more difficult pains.

FUTURE DIRECTION
REIRRADIATION

"In the past, most oncologists would find this an insurmountable problem with which to deal. However, with the development of new technologies including Intensity Modulated Radiation Therapy, Image Guided Radiation Therapy, Tomotherapy, Stereotactic Body Radiosurgical Techniques and Proton Beams opens entirely new vistas as to how best to handle these problems. Along with these technical developments has been a better understanding of altered fractionation technologies and how they might be used in developing a treatment program to previously irradiated volumes."

Luther W. Brady
Hans Peter Heilmann
Michael Molls

"Good doctors use both individual clinical expertise and the best available external evidence, and neither alone is enough. Without clinical expertise, practice risks becoming tyrannised by evidence, for even excellent external evidence may be inapplicable to or inappropriate for an individual patient. Without current best evidence, practice risks becoming rapidly out of date, to the detriment of patients."

BMJ1996 Jan 13;312(7023):71-2.
Evidence based medicine: what it is and what it isn't.
Sackett DL Rosenberg WM Gray JA Haynes RB Richardson WS.