Radioterapia stereotassica body nel paziente oligometastatico

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UOC Radioterapia Rieti

Review

2013

Stereotactic body radiotherapy for oligometastases

Alison C Tree, Vincent S K Khoo, Rosalind A Eeles, Merina Ahmed, David P Dearnaley, Maria A Hawkins, Robert A Huddart, Christopher M Nutting, Peter J Ostler, Nicholas J van As

"The role of radiotherapy in the management of metastatic disease has been mainly limited to palliation, but we now have an opportunity to challenge this idea…"

La incidenza della ***diffusione metastatica limitata*** non è stata ben studiata ma svariati dati suggeriscono che sia nota e frequente specie per alcuni tipi di tumori:

- Polmone
- Mammella
- Colon-retto
- Sarcomi

Nuove tecniche di imaging

Il miglioramento delle tecniche di imaging e del loro appropriato uso evidenzia in percentuale sempre superiore la presenza di metastasi asintomatiche

Aumento della percentuale di evidenza di condizione di malattia oligometastatica

Barney JD, Churchill EJ**: Adenocarcinoma of the kidney with metastasis to the lung cured by nephrectomy and lobectomy. J Urol 42:269-276, **1939

Caso di carcinoma renale con una metastasi al polmone trattato con nefrectomia e lobectomia. Il paziente muore dopo 23 anni senza recidiva di malattia

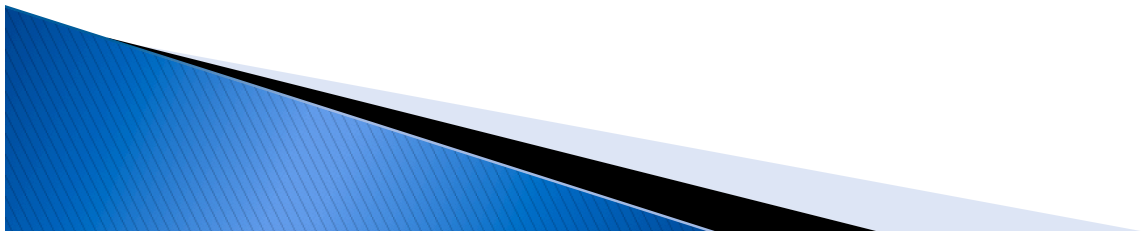


Table 1. Summary of Surgical Metastasectomy and SBRT for Metastasis Therapy to Multiple Sites

Surgical Series	Year	No. of Patients	5-Year Survival (%)	10-Year Survival (%)	Site
Rees et al (colorectal cancer)	2008	929	36[a]	23[a]	Liver
Fong et al (colorectal cancer)	1999	1,001	37	22	Liver
Pawlik et al (colorectal cancer)	2005	557	58	No 10-year follow-up	Liver
Carpizo et al (colorectal cancer)	2009	1,369		No 10-year follow-up	
Liver only		1,242	49		Liver
Limited EHD		127	26		Liver and EHD[b]
De Haas et al (colorectal cancer)	2008				Liver
R0 resection		234	61	43	
R1 resection		202	57	37	
Elias et al (colorectal cancer)	1998	269	24.7	No 10-year follow-up	Liver
Elias et al (noncolorectal only)	1998	147	36	No 10-year follow-up	Liver
Scheele et al (colorectal cancer)	1995	350	39.3	23.6	Liver
de Jong et al (colorectal cancer)	2009	1,669	47.3	No 10-year follow-up	Liver
Pastorino et al (many primary tumors)[c]	1997	4,572	36	26	Lung
Choong et al (soft tissue sarcoma)	1995	274	40	No 10-year follow-up	Lung
Casiraghi et al (many primary tumors)[d]	2011	575	46	No 10-year follow-up	Lung
Pfannschmidt et al (renal cell carcinoma)	2002	191	39.6	No 10-year follow-up	Lung
Pfannschmidt et al (colorectal cancer)	2003	167	32.4	10-year follow-up	Lung
Kanemitsu et al (colorectal cancer)	2003	313	38.3	No 10-year follow-up	Lung
Petersen et al (melanoma)	2007			No 10-year follow-up	Lung
Complete resection		249	21		
Incomplete resection		69	13		
Saito et al (colorectal cancer)	2002	165	39.6	37.2	Lung
Kim et al (multiple primary tumors)[e]	1998	37	24	No 10-year follow-up	Adrenal
Porte et al (NSCLC)	2001	43	11[f]	No 10-year follow-up	Adrenal
Mercier et al (NSCLC)	2005	23	23	No 10-year follow-up	Adrenal
Burt et al (NSCLC)	1992	185	13	7	Brain
Bonnette et al (NSCLC)	2001	103	11	No 10-year follow-up	Brain

serie chirurgiche hanno riportato ***favorevoli outcome clinici*** in pazienti con limitata estensione di malattia al fegato, polmone, surrenali e *cervello* ***evidenziando che una parte di pazienti con malattia limitata può essere curata con buone prospettive di risultato***

Outcomes after Resection of Synchronous or Metachronous Hepatic and Pulmonary Colorectal Metastases

2007

George Miller, MD, Peter Biernacki, BS, Nancy E Kemeny, MD, Mithat Gonen, PhD, Robert Downey, MD, FACS, William R Jarnagin, MD, FACS, Michael D'Angelica, MD, FACS, Yuman Fong, MD, FACS, Leslie H Blumgart, MD, FACS, Ronald P DeMatteo, MD, FACS

rates of 36% to 45%.[9-12] But the role of surgery in the management of patients who have both liver and lung metastases (either at the same or different times) is not well defined. In fact, development of both hepatic and pulmonary colorectal metastases is commonly regarded as an indicator of widespread tumor dissemination, and surgery is generally considered futile.

Unfortunately the benefits of resection and appropriate ***selection criteria*** in patients who develop metastasis are still poorly defined.

Radioterapia Stereotassica body

Perché SBRT ?

Motivo n° 1 un intervento radicale essere erogato durante una fase oligometastatica, potrebbe **modificare la progressione della malattia** nei pazienti che altrimenti sarebbero stati trattati palliativamente nella maggior parte dei casi

Motivo n° 2 Ritardare i successivi trattamenti

Motivo n° 3 La **corretta identificazione di un subset di pazienti oligometastatici** in cui la conseguente terapia ablativa consente **di modificare significativamente gli outcome clinici**

Radioterapia Stereotassica body

La SBRT di metastasi limitate ha mostrato promettenti tassi di **controllo locale** che vanno dal

65% ed il **96%**

Le **OS a 2 o 3 anni** riportate nelle varie casistiche sono comprese tra il

30% ed il **64%**

risultate comparabili con i dati della chirurgia .

La SBRT:

- Meno invasiva
- Può essere applicata ad un più largo numero di tumori, organi e sedi
- Sedi meno accessibili alla chirurgia
- A pazienti unfit per la chirurgia
- Meno costosa

Milano MT *et al Breast Cancer Res Treat 2009*

Kang JK et al *Clin Exp Metastasis 2010*

Salama JK et *al Cancer 2012*

Bae SH *et al J Surg Oncol 2012*

Radioterapia Stereotassica body

Radiation Series	Year	No. Patients	No. Lesions	Local Control (%)	Survival (%)	Site
Blomgren et al	1995	31	42	80	Not reported	Liver, lung, and retroperitoneum
Wulf et al	2004	41	51	80	33[g]	Lung
Hoyer et al (colorectal cancer)	2006	64	141	86[g]	38[g], 13[h]	Lung, liver, and adrenal
Hof et al	2007	61	71	63[i]	47.8[i]	Lung
Rusthoven et al	2009	47	63	92[g]	30[g]	Liver
Rusthoven et al	2009	38	63	96[g]	39[g]	Lung
Kang et al (colorectal cancer)	2010	59	78	66[i]	49[i]	Multiple
Okunieff et al	2006	49	125	83[i]	25[j]	Lung
Katz et al	2007	69	174	57[k]	24[l,m]	Liver
Lee et al	2009	70	143	71[m]	47[n]	Liver
Milano et al	2011	121				Multiple[p]
Breast cancer		39		87[o]	74[g], 47[o]	
All others		82		65[o]	39[g], 9[o]	
Salama et al	2011	61	111	66.7[g,q]	56.7[g]	Multiple
Bae et al (colorectal cancer)	2012	41	50	64[i], 57[h]	64[i], 38[h]	Lung, liver, and lymph node
Norihisa et al	2008	34		90[g]	84.3[g]	Lung

Studi retrospettivi

Radioterapia Stereotassica body

Table 2. Selected Ongoing Prospective Trials for Oligometastases

Trial Name or Number	Design	Eligibility	Intervention
SABR-COMET	Randomized	All metastatic sites treatable; maximum of three tumors to any single organ system; controlled primary tumor	Standard arm: palliative-scheme radiation; experimental arm: stereotactic ablative radiation
UPCI 10-028	Phase II	≤ Five metastases from solid malignancy	SBRT to affected sites
UPCI 10-027	Phase II	≤ Five metastases diagnosed at initial presentation	SBRT to affected sites in combination with treatment of primary tumor
NCT01565837	Phase II	Melanoma with ≤ five metastatic sites (not resectable)	Ipilimumab with SBRT to all sites, timed to be delivered before third cycle
NCT01185639	Phase II	NSCLC with ≤ five metastatic sites, involving lung, liver, adrenal, or spinal lesions; if primary untreated, must have ≤ three	SBRT to affected sites, delivered in three or five fractions
PulMiCC	Randomized	Pulmonary metastases from colorectal cancer	Standard: active monitoring; experimental: active monitoring with pulmonary metastasectomy

Abbreviations: NSCLC, non–small-cell lung cancer; PulMiCC, Pulmonary Metastasectomy in Colorectal Cancer; SABR-COMET, Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors; SBRT, stereotactic body radiotherapy; UPCI, University of Pittsburgh Cancer Institute.

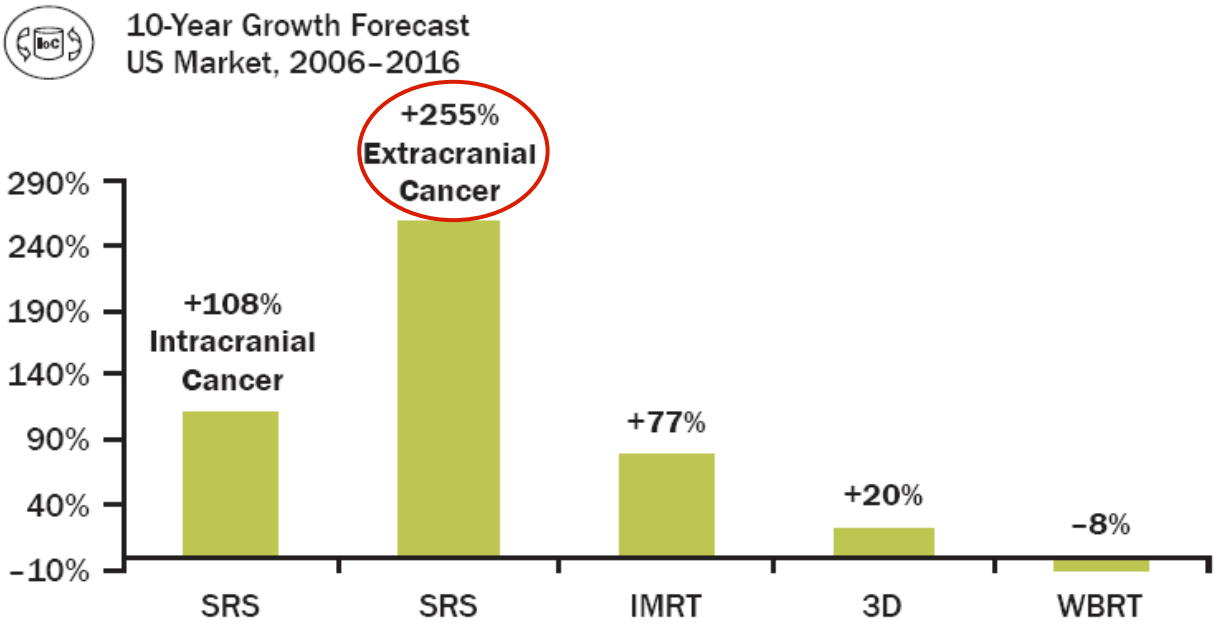
Studi prospettici in corso

Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET).
Radiosurgery for Patients Recurrent Oligometastatic Disease. Radiosurgery for Patients With Oligometastatic Disease at Initial Presentation.

Concurrent Ipilimumab and Stereotactic Ablative Radiation Therapy (SART) for Oligometastatic But Unresectable Melanoma. http://clinicaltrials.gov/

Radiosurgery is growing for the treatment of non-neurological tumors.

- Breast
- Liver
- Lung
- Pancreas
- Prostate
- Rectum
- Spine



Data from "US Clinical Intelligence Report 2007"

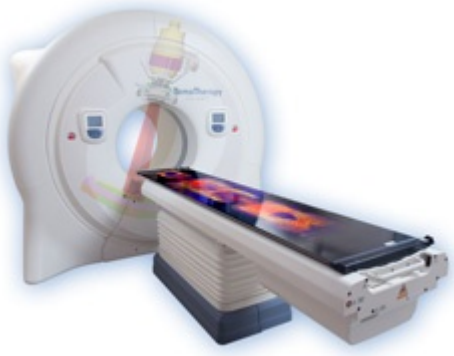
SBRT Linac-based

Trilogy

Vero

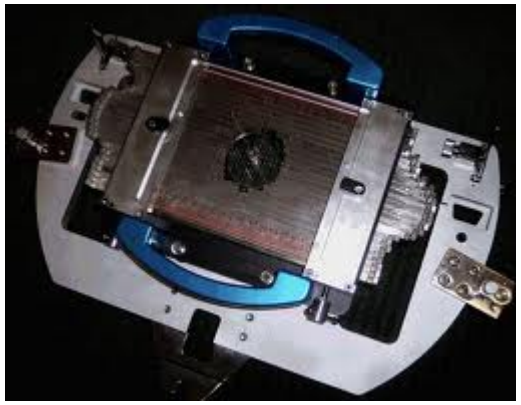
Cyberknife

Tomotherapy



SBRT: LINAC dedicato o modificato?

- Aumenta le applicazioni del LINAC con maggiore focalizzazione e precisione spaziale



SBRT

I miglioramenti hight tech sono riferiti all'affinamento dell' *approccio balistico*:

. intensità modulata comprendente arcoterapia ed approcci rotazionali
. possibilità di target multipli
. bracci robotici CyberKnife Robotic Radiosurgery

- Dosi sempre più alte al target ed in poche sedute
- GTV= CTV PTV= GTV + margine millimetrico
- Dosi sempre più basse ai tessuti sani
- Effetti accettabili sulle strutture critiche

Radioterapia Stereotassica body

Approccio tecnico

- ✓ Miglioramento della fase di identificazione dei contorni della lesione
- ✓ adeguata immobilizzazione e riposizionamento del paziente
- ✓ corretta collocazione del volume da trattare nei 3 assi dello spazio (fiducials, body-frame, riflettori optoelettronici, OBI , cone beam CT etc.)
- ✓ adeguato controllo della organ motion respiratoria per la massima riduzione dei margini interni.

Song 2004, Timmerman 2005

Controllo del Respiratory Motion

Dampening or inibitory techniques

La ***compressione addominale obbliga il paziente ad usare solo la gabbia toracica per respirare,*** con conseguente riduzione del movimento complessivo intratoracico

Vantaggi: semplice, nessuna pausa nell'erogazione della RT, non necessita di particolari tecnologie, è la tecnica più usata

Svantaggi: disconfort per il pz., non estremamente preciso (escursioni del target anche di 0.5-1 cm)

Controllo del Respiratory Motion

L'active breath control (ABC),

è un'altra forma di ***inibizione del respiro, ma controllata dal pz. stesso***. Il trattamento viene erogato solo durante alcune fasi del respiro del paziente (ispirazione, fase del respiro in cui il polmone è più stirato e quindi il tessuto sano è più lontano)

Svantaggi: training del paziente, allungamento dei tempi di RT

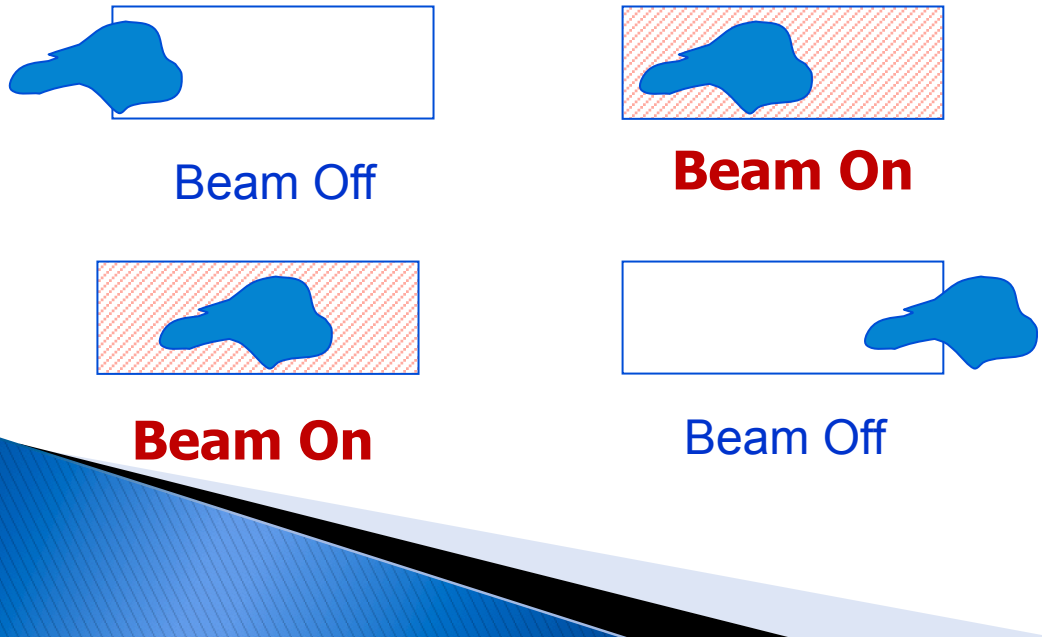
Controllo del Respiratory Motion

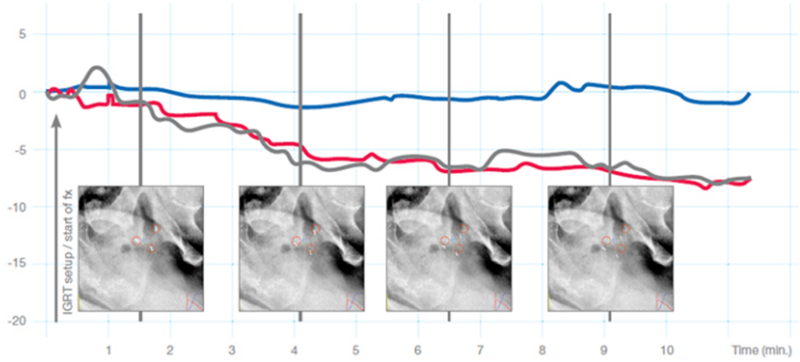
Gating systems

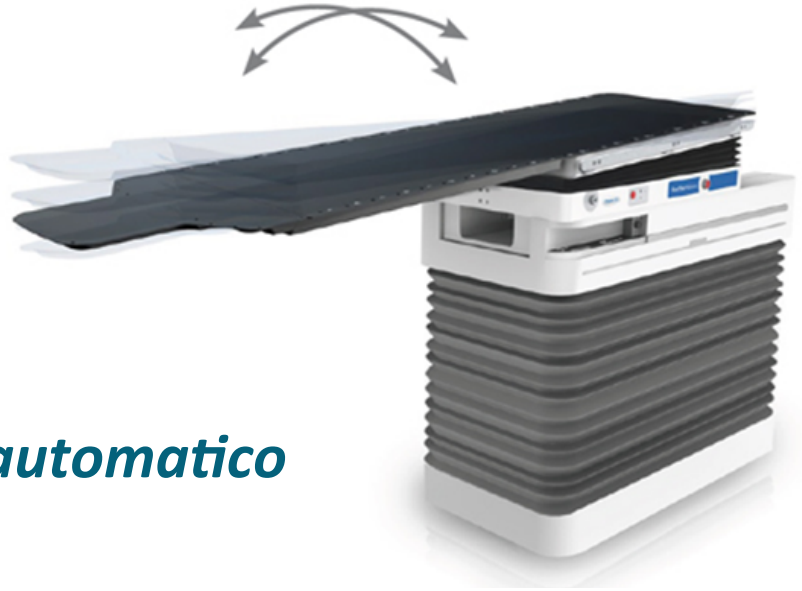
- La macchina seguendo il ciclo respiratorio del paziente, eroga RT in genere in espirazione (fase più lunga del ciclo), e si ferma quando il pz. inspira.

Vantaggi: maggiore compliance e confort per il pz.

Svantaggi: allungamento dei tempi, maggior rischio di tox per tessuti sani (< stiramento polmone con < distanza tumore/tessuti sani).







Riposizionamento automatico

Controllo del Respiratory Motion

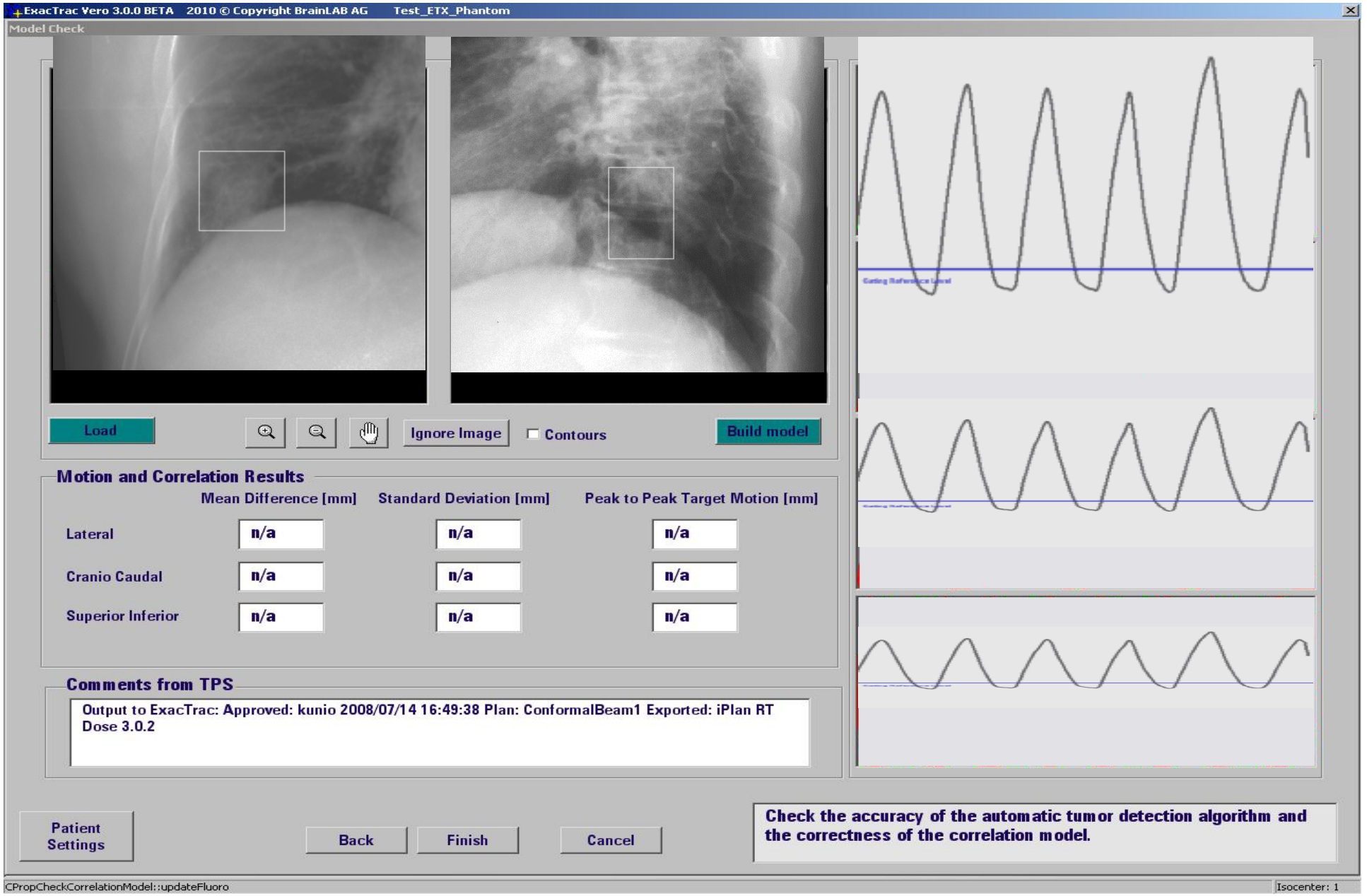
Tracking systems

Prevedono la possibilità che il fascio possa seguire continuamente il target nel suo movimento, ad esempio come fa cyberknife o Vero , o attraverso un collimatore dinamico che modifica continuamente la posizione delle lamelle.

Vantaggi: erogazione continua di RT

Svantaggi: rischio di movimenti incontrollati e di "ritardi" della macchina nel seguire il target.

DYNAMIC TUMOR TRACKING

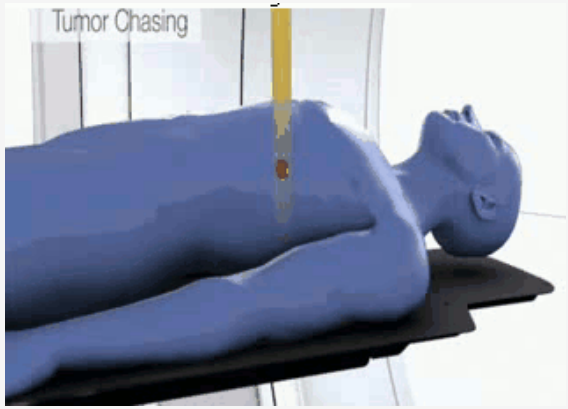


DYNAMIC TUMOR TRACKING

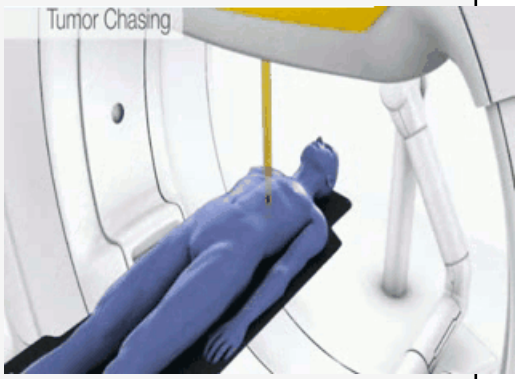
PATIENT TREATMENT

Mode 1

Mode 2



Tracking based on IR breathing signal.



Real-time tumor tracking

Radioterapia Stereotassica body

Fattori che influenzano il controllo locale ,PFS ed OS

Tossicità dei trattamenti

SRBT : Fattori che influenzano il controllo locale ,PFS ed OS

1) Numero delle metastasi

1 a 3 metastasi	**9 mesi**	Miglior PFS	46% ulteriore diffusione metastatica
4 o 5 metastasi		Peggiore PFS	75% ulteriore diffusione metastatica

Salama et al *Cancer 2011*

Cancer. 2012 Jun 1;118(11):2962-70. doi: 10.1002/cncr.26611. Epub 2011 Oct 21.

Stereotactic body radiotherapy for multisite extracranial oligometastases: final report of a dose escalation trial in patients with 1 to 5 sites of metastatic disease.

Salama JK, Hasselle MD, Chmura SJ, Malik R, Mehta N, Yenice KM, Villaflor VM, Stadler WM, Hoffman PC, Cohen EE, Connell PP, Haraf DJ, Vokes EE, Hellman S, Weichselbaum RR.

2) Istologia

Breast cancer

PFS	*a 2 aa*	***36% vs 13%*** *altri tumori*
OS	*a 6 aa*	***49% vs 9 %*** *altri tumori*
LC	*a*	***87% vs 74%*** *altri tumori*

Milano et al *IJROBP 2012*

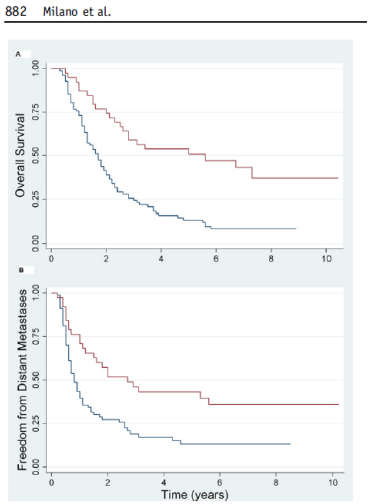


Fig. 1. Kaplan-Meier actuarial (A) overall survival and (B) freedom from distant progression for breast cancer (red line) and nonbreast cancer (blue line) patients. A color version of this figure is available at www.redjournals.com.

SRBT : Fattori che influenzano il controllo locale ,PFS ed OS

3) Sede

*Una revisione retrospettiva di pazienti con **metastasi confinata a un organo** ha dimostrato che quelle **ossee** o **linfonodali toraciche** hanno una migliore sopravvivenza di quelle polmonari o epatiche, e che tendono anche ad avere una migliore sopravvivenza libera da progressione.*

Milano MT et al *AJCO 2010*

- **La sede più o meno critica della metastasi** condiziona a volte il risultato terapeutico condizionando la possibilità di erogare dosi elevate

4) Disease-free interval

*Se **tempo della recidiva***	*> 12 mesi*	*OS a 3 aa*	*53%*
	< 12 mesi	*OS*	*19%*

Inoue et al *Jpns JCO 2010*

Se DFS > 12 mesi OS superiore HR 0.51, 95%

Zhang et al *Chin Med J 2011*

SRBT : Fattori che influenzano il controllo locale ,PFS ed OS

5) Diametro

Il diametro della metastasi è predittivo del controllo " in field "

Choi et al *IJROBP 2009*

Il controllo in field è inversamente proporzionale al diametro della metastasi

Milano et al *IJROBP 2012*

Metastasi epatiche

< 3 cm controllo del 100% a 2 anni

➢3 cm controllo del 77%

Rusthoven et al *JCO 2009*

6) Dose e Volumi di contornazione

Diversi Modelli investigativi

Dosi e frazioni differenti per organi ed apparati differenti

SRBT : Fattori che influenzano il controllo locale ,PFS ed OS

5) Diametro

Il diametro della metastasi è predittivo del controllo " in field "

Choi et al *IJROBP 2009*

Il controllo in field è inversamente proporzionale al diametro della metastasi

Milano et al *IJROBP 2012*

Metastasi epatiche

< 3 cm controllo del 100% a 2 anni

➢3 cm controllo del 77%

Rusthoven et al *JCO 2009*

6) Dose e Volumi e metodi di contornazione e finalità

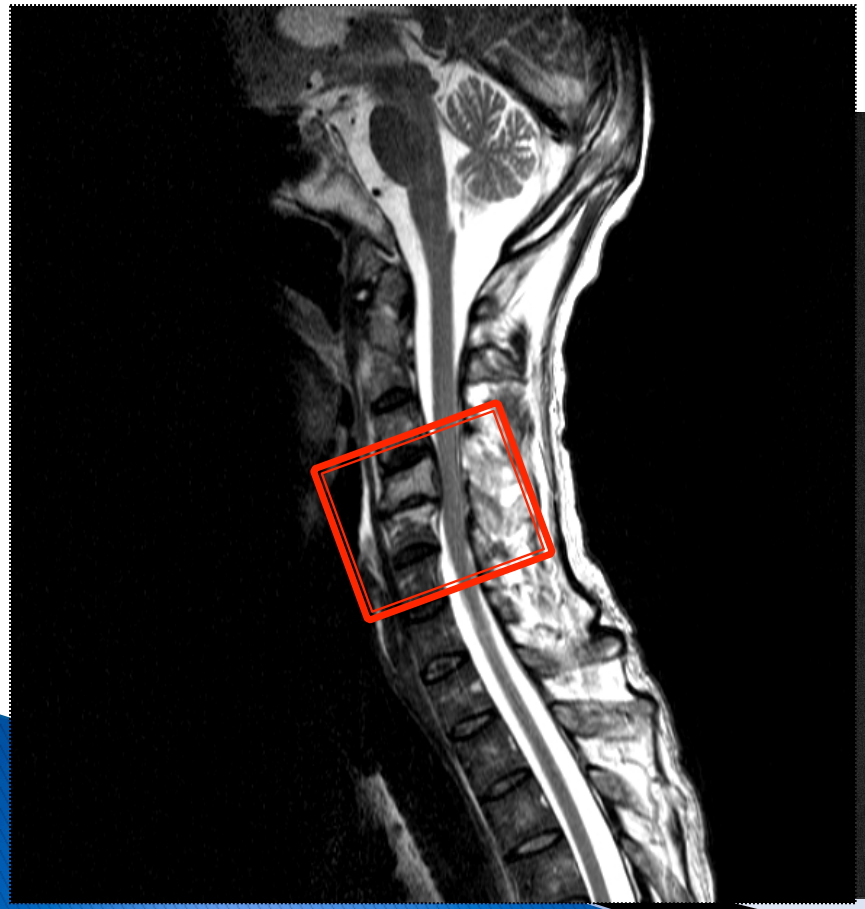
Il CTV della SBRT è in genere diverso (minore) rispetto alla 3D-CRT

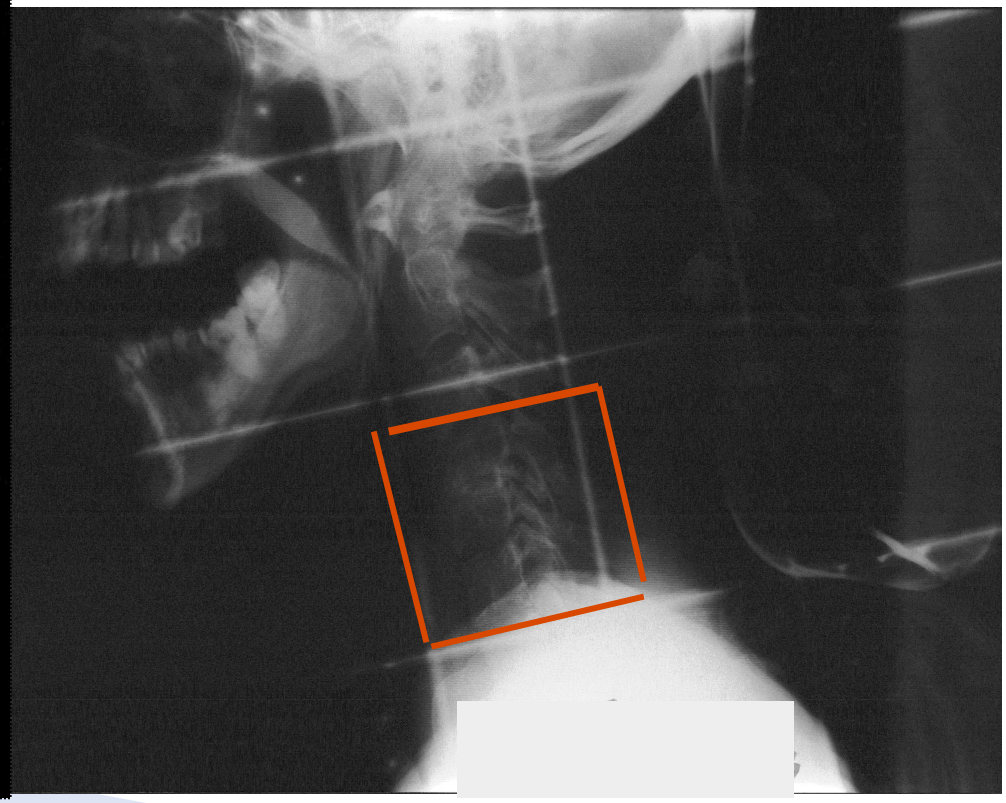
Es: metastasi vertebrale

Perché fare SBRT e non 3D?

- Dose ablativa e non palliazione (malattia non diffusa)
- Metastasi da primitivo radioresistente
- Malattia confinata ad una parte della vertebra
- Pregressa chemioterapia (mielotossicità)
- Reirradiazione

Tecnica d'irradiazione





2012

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Central Nervous System Tumor

International Spine Radiosurgery Consortium Consensus Guidelines for Target Volume Definition in Spinal Stereotactic Radiosurgery

Brett W. Cox, MD,*,[1] Daniel E. Spratt, MD,*,[1] Michael Lovelock, PhD,[†] Mark H. Bilsky, MD,[‡] Eric Lis, MD,[§] Samuel Ryu, MD,[‖] Jason Sheehan, MD,[¶] Peter C. Gerszten, MD, MPH,** Eric Chang, MD,[††] Iris Gibbs, MD,[‡‡] Scott Soltys, MD,[‡‡] Arjun Sahgal, MD,[§§] Joe Deasy, PhD,[†] John Flickinger, MD,[‖‖] Mubina Quader, PhD,[‖‖] Stefan Mindea, MD,[¶¶] and Yoshiya Yamada, MD[‡‡]

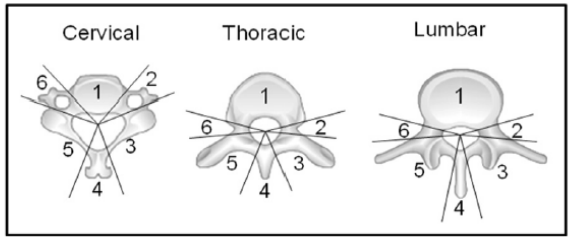


Fig. 1. International Spine Radiosurgery Consortium anatomic classification system for consensus target volumes for spine radiosurgery.

Table 4 Summary of contouring guidelines for GTV, CTV, and PTV in spinal stereotactic radiosurgery

Target volume	Guidelines
GTV	• Contour gross tumor using all available imaging • Include epidural and paraspinal components of tumor
CTV	• Include abnormal marrow signal suspicious for microscopic invasion • Include bony CTV expansion to account for subclinical spread • Should contain GTV • Circumferential CTVs encircling the cord should be avoided except in rare instances where the vertebral body, bilateral pedicles/lamina, and spinous process are all involved or when there is extensive metastatic disease along the circumference of the epidural space without spinal cord compression
PTV	• Uniform expansion around CTV • CTV to PTV margin $\leq$3 mm • Modified at dural margin and adjacent critical structures to allow spacing at discretion of the treating physician unless GTV compromised • Never overlaps with cord • Should contain entire GTV and CTV

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.

SRBT : Fattori che influenzano il controllo locale ,PFS ed OS

7) Timing ?

Fumagalli *et al. Radiation Oncology* 2012, **7**:164
http://www.ro-journal.com/content/7/1/164

2012

RADIATION ONCOLOGY

RESEARCH Open Access

A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases

Ingrid Fumagalli[1], Jean-Emmanuel Bibault[1], Sylvain Dewas[1], Andrew Kramar[2], Xavier Mirabel[1], Bernard Prevost[1], Thomas Lacornerie[1], Hajer Jerraya[3] and Eric Lartigau[1*]

SBRT and previous chemotherapy regimens

We wondered whether or not pre-treated patients with metastatic disease could benefit from SBRT. Most of our patients had received prior chemotherapy (91%), with a high number of chemotherapy regimens, 27% of them receiving more than three regimens, which may have increased the radioresistance of the metastases. We found that a patient's history of prior chemotherapy was a major risk factor in recurrence outside the treatment volume (HR = 4.51, 95% CI: 1.10–18.47, p = 0.007). Also, the number of previous chemotherapy regimens

SRBT : Fattori che influenzano il controllo locale ,PFS ed OS

7) SBRT e CHT: timing ?

Fumagalli *et al. Radiation Oncology* 2012, **7**:164
http://www.ro-journal.com/content/7/1/164

RADIATION ONCOLOGY

RESEARCH **Open Access**

A single-institution study of stereotactic body radiotherapy for patients with unresectable visceral pulmonary or hepatic oligometastases

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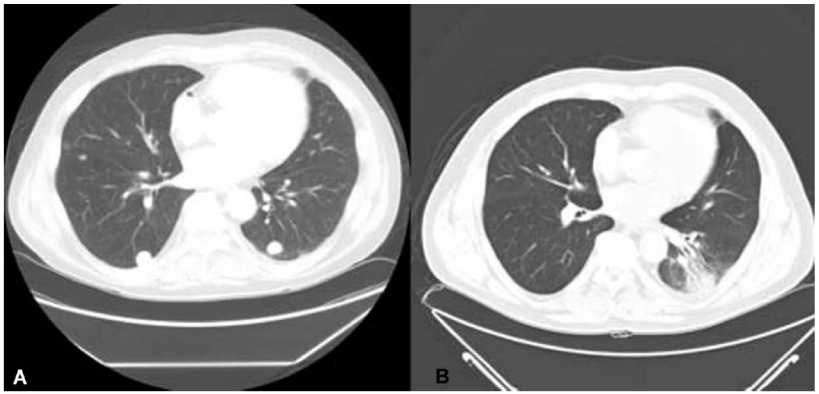
administered or progression while receiving chemotherapy significantly correlates with a higher risk of failure. One hypothesis that could explain this finding could be that the previous chemotherapy regimens, received by the patients, selected tumoral clones with a lower sensitivity to radiation, even if no study has been published to prove it. This suggests that SBRT should perhaps be used as a local treatment for metastases before the administration of several systemic therapies.

TUMOR RADIOTHERAPY

Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2: Tumor and Immunological Responses

Steven K. Seung,[1,2]* Brendan D. Curti,[1,3]*† Marka Crittenden,[1,2] Edwin Walker,[1]



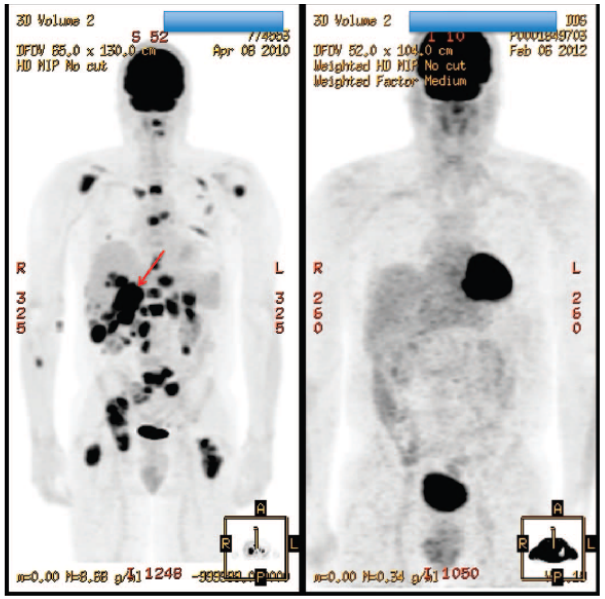


Fig. 2. Before and after PET imaging in a patient with widely metastatic melanoma. Two liver lesions were treated with SBRT.

12 casi di melanoma e ca renale
SBRT 20 Gy x 3 3/7 gg prima della IL2

SBRT max 3 localizzazioni dmt max 7 cm

8 paz (66.6%) RC o PR
1 paz stabile
3 pazienti in progressione

> CD4 – CD8 after

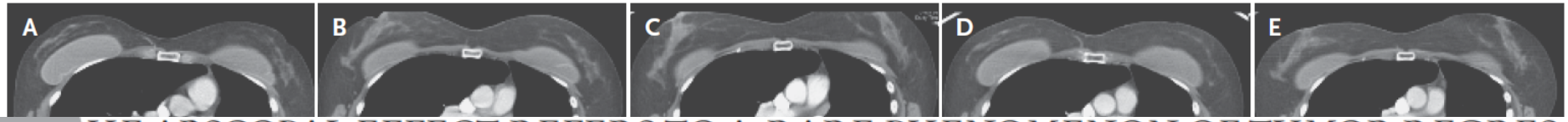
•Gli autori combinano IL-2 ad alte dosi RT stereotassica in base ad osservazioni cliniche di aumentata efficacia nei pazienti anche se deve ancora essere provata l'ipotesi secondo cui il **danno radio indotto induce il rilascio di antigeni tumorali e modifiche del microambiente capaci di aumentare l'effettoimmuno-attivante dell'IL-2.**

The NEW ENGLAND JOURNAL of MEDICINE

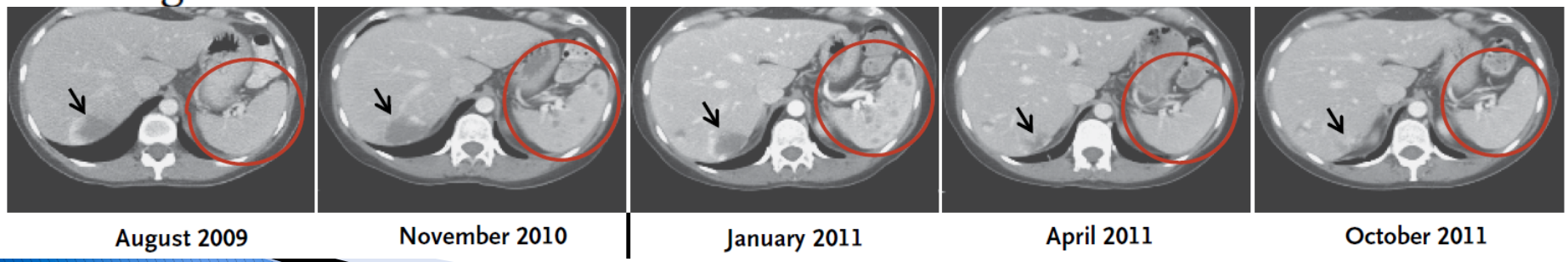
2012

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma



THE ABSCOPAL EFFECT REFERS TO A RARE PHENOMENON OF TUMOR REGRESsion at a site distant from the primary site of radiotherapy.[1] Localized radiotherapy has been shown to induce abscopal effects in several types of cancer, including melanoma, lymphoma, and renal-cell carcinoma.[2-4] The biologic characteristics underlying this effect are not completely understood, but it may be mediated by immunologic mechanisms.[5]



SRBT and abscopal effect

1) esaltazione della risposta immunitaria dell'ospite "innate ed adaptive"

2) incrementa la produzione di un interferon gamma peptide reattivo tumorale che produce cellule immunitarie antitumorali e la loro diffusione verso il drenaggio linfatico del tumore

Lugade AA et al: *Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. J Immunol 2005*

3) Attivazione di TLR 4 attraverso proteine tumorali

Apetoh L et al: *Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. Nat Med 2007*

4) Attivazione e immissione di CD8 T cell nel drenaggio linfatico (dopo 20 Gy con stereobody)

Lee Y et al: *Therapeutic effects of ablative radiation on local tumor require CD8 T cells: Changing strategies for cancer treatment. Blood 2009*

Concurrent Ipilimumab and Stereotactic Ablative Radiation Therapy (SART) for Oligometastatic But Unresectable Melanoma. http://clinicaltrials.gov/

SBRT Metastasi polmonari e tox

The Oncologist

Table 1. Outcomes of stereotactic body radiation therapy for lung metastases from selected trials

Study	*n* of patients	Median dose/*n* of fractions	Median (range) follow-up, mos	Local control rate	Overall survival	Toxicity
Onimaru et al. [5]	45	48 Gy/8; 60 Gy/8	18 (2–44)	3-yr, 69.6% for 48 Gy, 100% for 60 Gy	2-yr, 47.1%	Grade 5, 1 (2.2%)
Wulf et al. [32]	27	30 Gy/3; 36 Gy/3	13–17	2-yr, 71%	1-yr, 48% 2-yr, 21%	Grade 3, 1 (3.7%) Grade 5, 1 (3.7%)
Yoon et al. [71]	53	30 Gy/3; 40 Gy/4; 48 Gy/4	14 (4–56)	70% for 30 Gy, 77% for 40 Gy, 100% for 48 Gy	1-yr, 89%; 2-yr, 51%	Grade ≥2, 0%
Okunieff et al. [18]	50	50 Gy/10; 48 Gy/6; 57 Gy/3	18.7 (3.7–60.9)	3-yr, 91%	2-yr, 50%	Grade 2, 6.1% Grade 3, 2%
Norihisa et al. [6]	34	48 Gy/4; 60 Gy/5	27 (10–80)	2-yr, 90%	2-yr, 84%	Grade 2, 4 (12%) Grade 3, 1 (3%)
Brown et al. [72]	35	5 Gy/1 to 60 Gy/4	18 (2–41)	Crude, 77%	2-yr, 72.5%	Grade 3–4, 1 (2.8%)
Rusthoven et al. [14]	38	60 Gy/3	15.4 (6–48)	2-yr, 96%	2-yr, 39%	No grade 4 Grade 3, 3 (8%)
Ricardi et al. [17]	61	45 Gy/3; 26 Gy/1	20.4 (3–77)	2-yr, 89%	2-yr, 66.5	Grade 3, 1 (1.6%)

Original article

Central thoracic lesions treated with hypofractionated stereotactic body radiotherapy

Michael T. Milano *, Yuhchyau Chen, Alan W. Katz, Abraham Philip, Michael C. Schell, Paul Okunieff

Department of Radiation Oncology, University of Rochester Medical Center, NY, USA

Institution	Patient population	Prescribed dose (Gy)	Fraction dose (Gy)	BED2 (Gy)	Toxicity
IndianaU.	Stage I NSCLC	60-66	**20-22**	219-258	11-Fold increase risk of severe-fatal toxicity
Hokkaido U	NSCLC and Mts	48	**6**	64	1 of 9 with severe toxicity
U. Texas, San Antonio	NSCLC and Mts	36	**6-12**	86-126	1 of 9 – asymptomatic airway collapse
Air Force General Hospital	Stage I-II NSCLC	60-70 40-50	**6-7** **4-5**	120-167	No severe toxicity
VU Amsterdam	Stage I NSCLC	60	**7.5**	88	No severe toxicity
Technical U.	NSCLC and Mts	35	**7**	105	No severe toxicity

Moderately hypofractionated SBRT to central thoracic lesions is effective with respect to local control and toxicity.

Radiother Oncol, 2009

TOSSICITA' *Polmonite attinica 3D o SBRT*

Early phase – radiation pneumonitis (dispnea, tosse, febbricola, fastidi)

non apprezzabile fino a 30 Gy

1-6 mesi dal termine della RT

Furuse 1999 Choi 2004

Later phase – radiation fibrosis (tosse, cuore polmonere)

Deposizione di collagene

Da 6 A 12 mesi dal termine della RT

Koenig 2002 Linda 2009

Tre fasi sequenziali:

1) Fase acuta essudativa

2) Fase proliferativa e di organizzazione

polmonite

Infiltrazione più o meno organizzata di macrofagi

3)Fase cronica con fibrosi

Deposizione progressiva di collagene

Park 2000

Simile alla BOOP

Tossicità polmonare dopo RT
Variabili

Legate al trattamento

Dose (il tempo di insorgenza di una tox 3D è similare alla RT convenzionale; per la SBRT cresce invece la probabilità di un danno tardivo)
Frazione volume
Tipologia del trattamento
V20 (4% per SBRT - 30/35% per 3D)

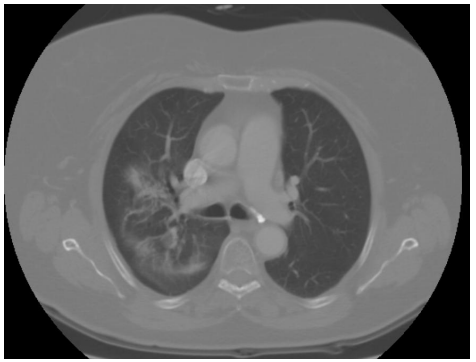
Legate al paziente

PS
Patologie polmonari
Pregressa Chemioterapia
Pregressa RT
Sede (centrale o periferica)

Lopez 2007

TOSSICITA'Modificazioni radiologiche precoci (entro 6 mesi) (Classificazione Ikezoe)

- Diffuse consolidation 20-30%
  (consolidation more than 5 cm in largest dimension)
- Patchy consolidation 8-22%
  (consolidation less than 5 cm in largest dimension)
- Diffuse ground glass opacities 4-8%
  (more than 5 cm of GGO)
- Patchy ground glass opacities 10-15%
  (less than 5 cm of GGO)



Diffuse ground glass opacities

Tossicità polmonari precoci dopo RT

Le alterazioni visibili alla TC dopo SBRT o 3D sono differenti rispetto alla radioterapia convenzionale . Differiscono in:

1) Caratteristiche morfologiche
2) Estensione
3) Distribuzione

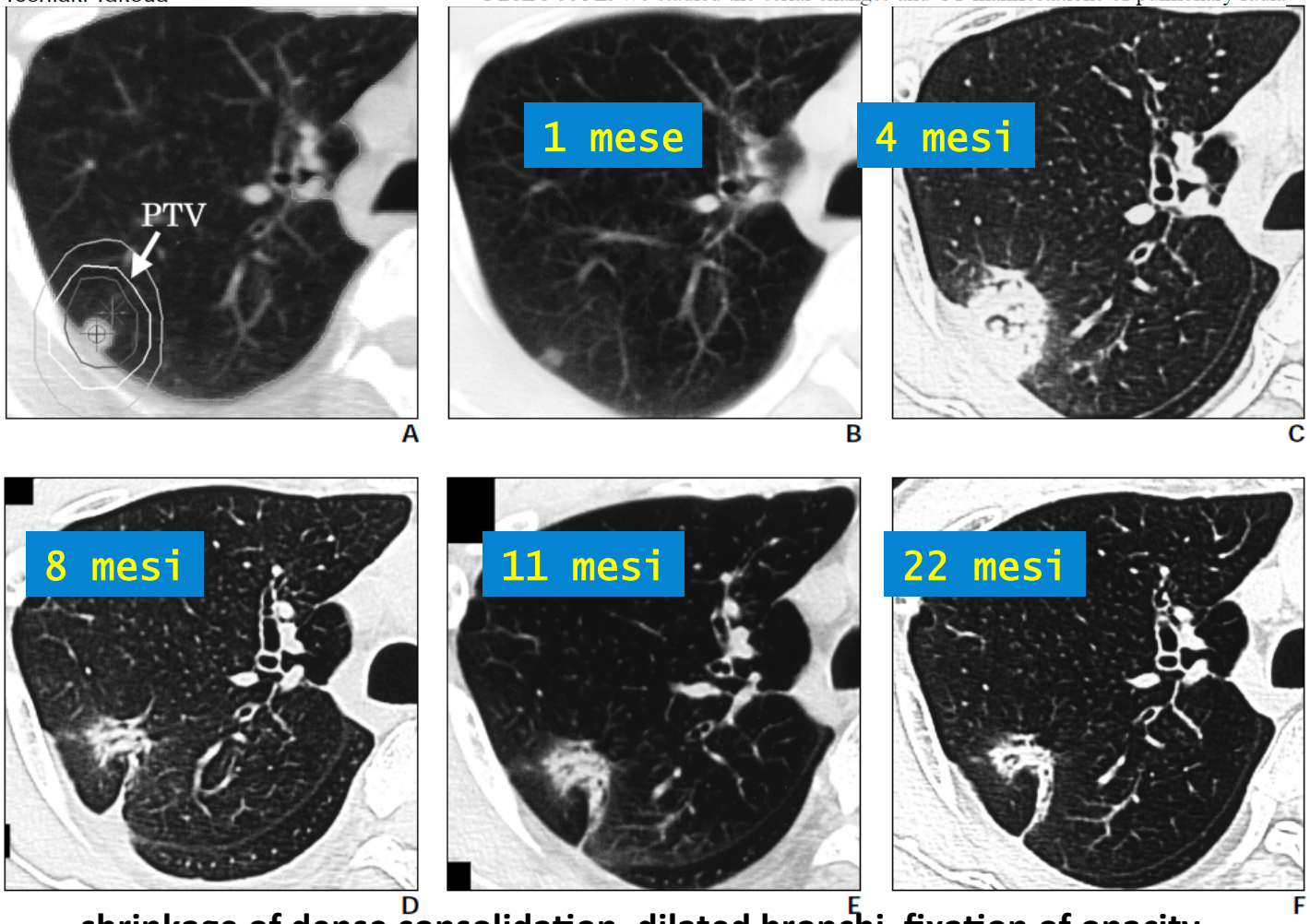
3D focale o nodulare opacità vetro smerigliato aree di consolidazione o entrambe con ***reperti situati immediatamente intorno al tumore trattato***
In altri casi i reperti radiologici ***possono essere localizzati al di fuori del target***, anche se confinati all'interno del campo di irradiazione

SBRT Le alterazioni radiologiche sono visibili ***solo all'interno del target*** a causa dell'alto gradiente di dose

Radiation Injury After Hypofractionated Stereotactic Radiotherapy for Peripheral Small Lung Tumors: Serial Changes on CT

Toshiaki Takeda[1] AJR 2006

OBJECTIVE. We studied the serial changes and CT manifestations of pulmonary radia



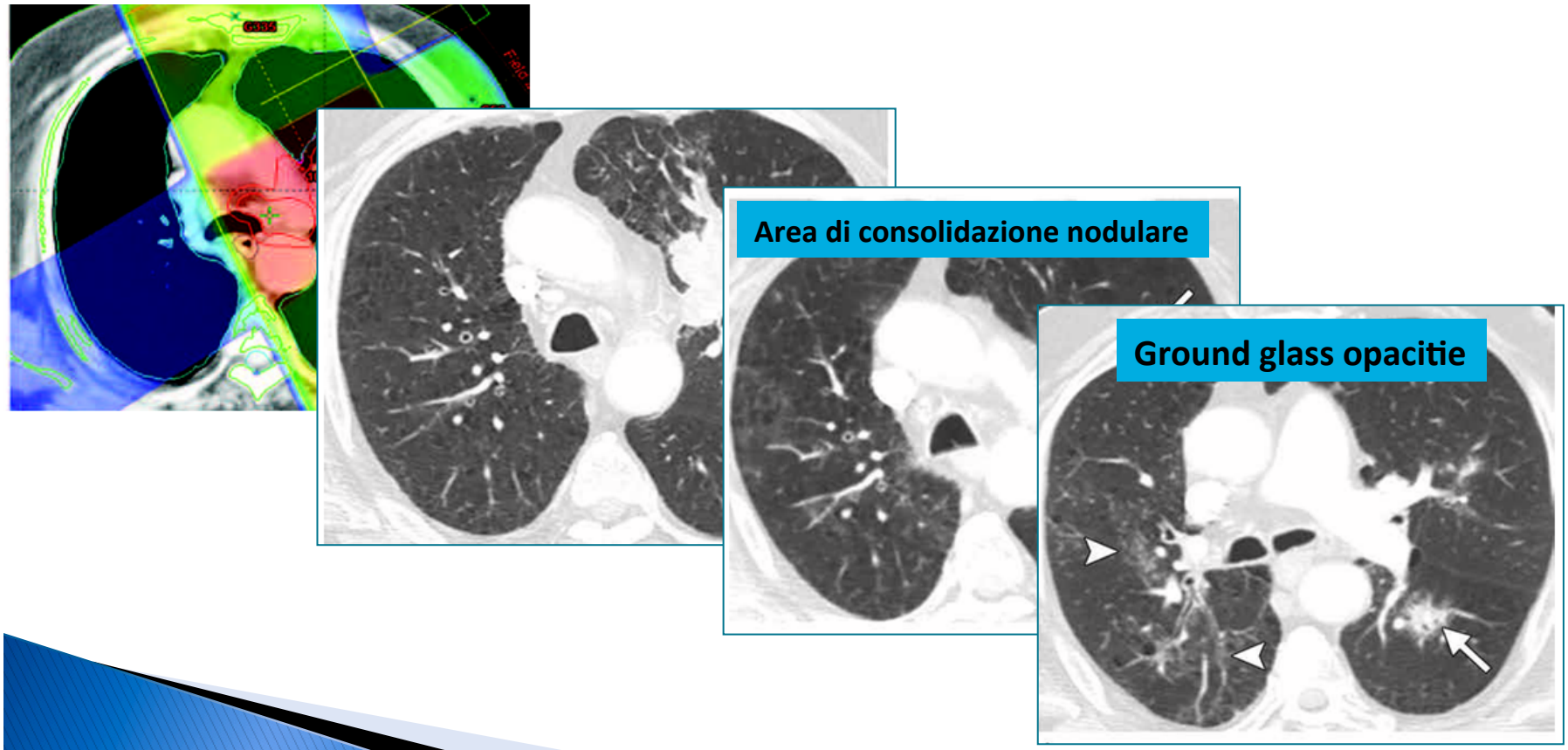
Patchy ground-glass opacity.

shrinkage of dense consolidation, dilated bronchi, fixation of opacity

CHEST IMAGING

2011

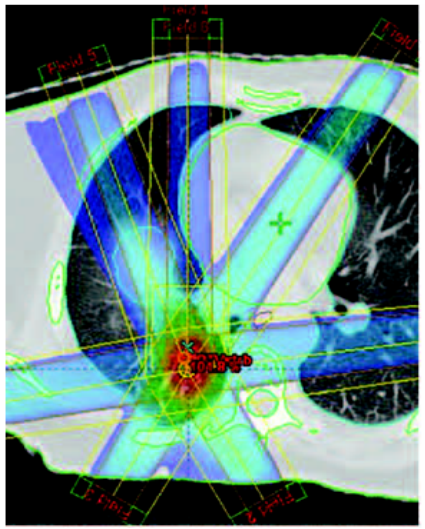
Lung Abnormalities at Multimodality Imaging after Radiation Therapy for Non–Small Cell Lung Cancer 1

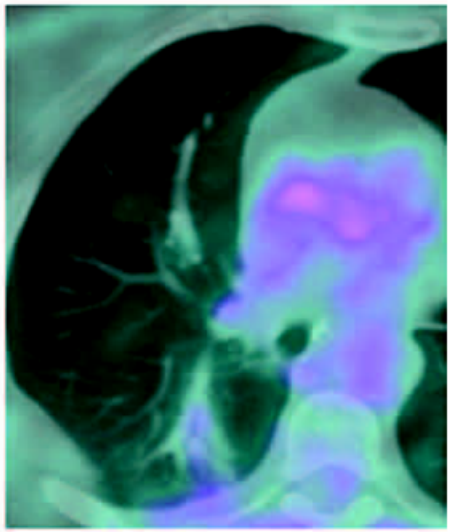


CHEST IMAGING

2011

Lung Abnormalities at Multimodality Imaging after Radiation Therapy for Non–Small Cell Lung Cancer 1





2 mesi

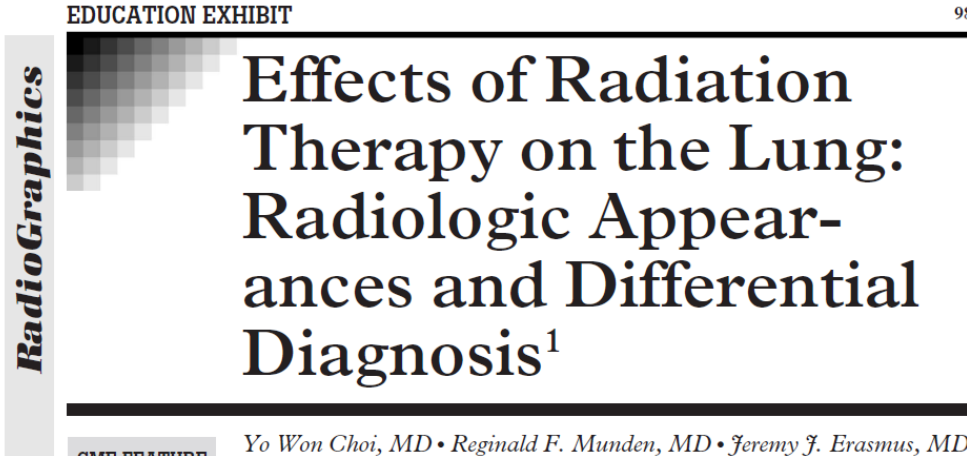
9 mesi

Diffusa consolidazione

Retrazione della consolidazione

TOSSICITA' Modificazioni radiologiche tardive (oltre 6 mesi)

2011


EDUCATION EXHIBIT

RadioGraphics

Effects of Radiation Therapy on the Lung: Radiologic Appear-ances and Differential Diagnosis[1]

Yo Won Choi, MD • Reginald F. Munden, MD • Jeremy J. Erasmus, MD

- Area ben definita di regressione tumorale
- Cicatrici lineari (linear scarring)
- Aree di consolidamento
- Bronchiectasie da trazione
- Movimenti verso l'ilo

TOSSICITA ’Modificazioni radiologiche tardive

2002

Radiation Injury of the Lung After Three-Dimensional Conformal Radiation Therapy

Titus R. Koenig[1]

OBJECTIVE. The objective of this study is to describe the CT patterns of radiation injury in the

Fibrosi radioindotta

- Modified conventional pattern
- Mass-like pattern
- Scar-like pattern

TOSSICITA ’Modificazioni radiologiche tardive

2002

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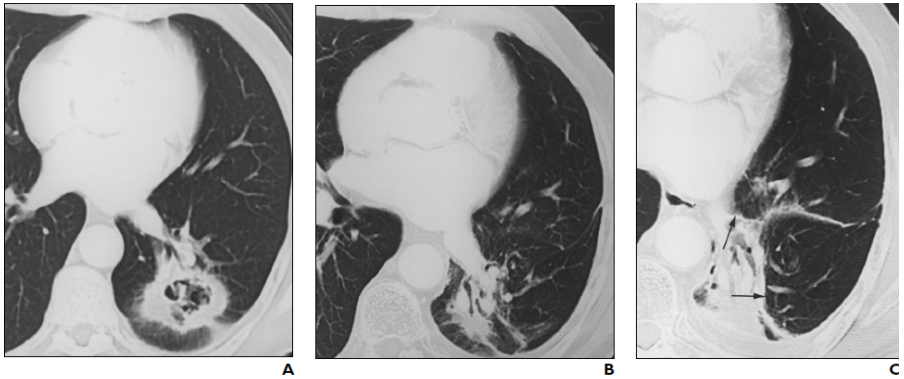

Fig. 3.—Modified conventional pattern in 81-year-old man with squamous cell carcinoma.
A, Pretreatment CT scan shows cavitary mass in left lower lobe.
B, CT scan obtained 10 months after completion of radiation therapy shows decrease in size of mass and development of consolidation indicating organizing fibrosis.
C, CT scan obtained 22 months after completion of radiation therapy shows well-defined area (*arrows*) of consolidation, volume loss, and traction bronchiectasis typica of radiation fibrosis. Note lung anterior to fibrosis is normal.

- **Opacità a margini netti**
- **Perdita di volume**
- **Bronchiectasie da trazione**
- ***Minore estensione rispetto alla RT convenzionale***
- **Può modificarsi la localizzazione nel primo anno di comparsa con dislocazione verso l’ilo o lontano dall’ilo**

TOSSICITA ’Modificazioni radiologiche tardive

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- Scar-like pattern

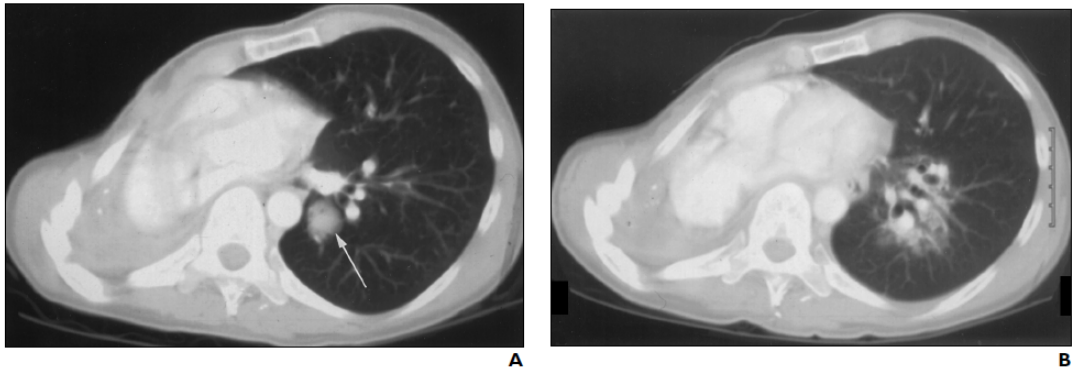


Fig. 4.—Masslike pattern in 44-year-old woman with adenoid cystic carcinoma. Note right pneumonectomy.
A, Pretreatment CT scan shows well-circumscribed mass (*arrow*) in left lower lobe.
B, CT scan obtained 21 months after completion of radiation therapy shows consolidation and bronchiectasis at tumor site that resembles mass.

- **Aree di consolidazione focale situata *2 cm* oltre il tumore**
- **Corrisponde alla zona con più alta dose**
- **Può modificarsi la localizzazione nel primo anno di comparsa con dislocazione verso l’ilo o lontano dall’ilo**

TOSSICITA ’Modificazioni radiologiche tardive

2002

Radiation Injury of the Lung After Three-Dimensional Conformal Radiation Therapy

Titus R. Koenig[1]

OBJECTIVE. The objective of this study is to describe the CT patterns of radiation injury in the

Fibrosi radioindotta

- Modified conventional pattern
- Mass-like pattern
- **Scar-like pattern (cicatrice)**

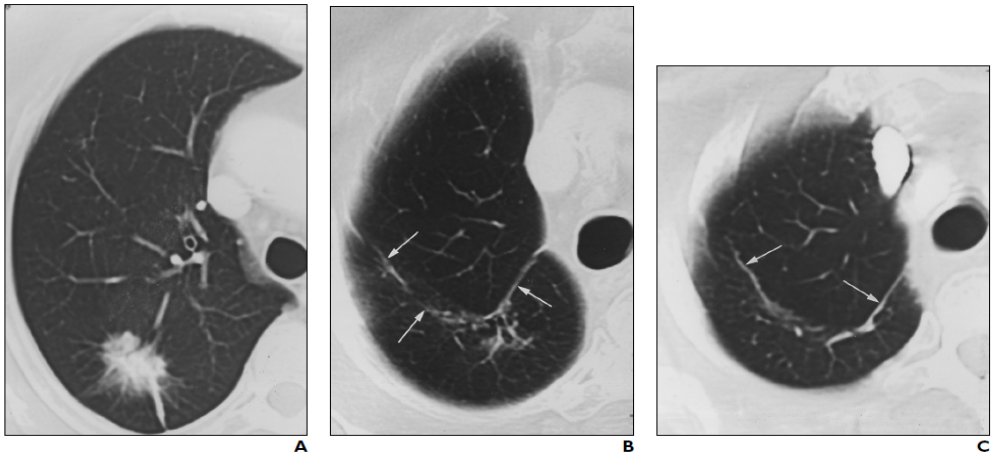


Fig. 5.—Scarlike pattern in 60-year-old woman with adenocarcinoma.
A, Pretreatment CT scan shows spiculated lesion in right upper lobe.
B, CT scan obtained 11 months after radiation therapy shows linear area of consolidation (*arrows*) with volume loss and no evidence of residual tumor.
C, CT scan obtained 36 months after completion of radiation therapy shows only linear band (*arrows*) that resembles scar.

- **Opacità lineari ampie < 1 cm**
- **Perdita di volume moderata o cospicua e che rimane presente alla TC nel sito del tumore quando questo è completamente o quasi completamente scomparso**

TOSSICITA ’Modificazioni radiologiche tardive

2002

Radiation Injury of the Lung After Three-Dimensional Conformal Radiation Therapy

Titus R. Koenig[1]

OBJECTIVE. The objective of this study is to describe the CT patterns of radiation injury in the

Fibrosi radioindotta

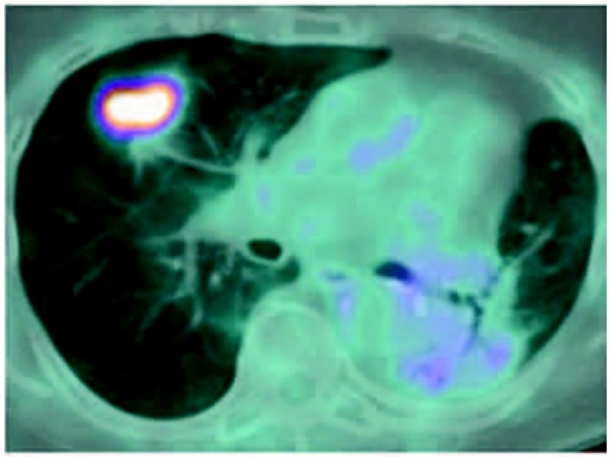
- Modified conventional pattern
- Mass-like pattern
- Scar-like pattern

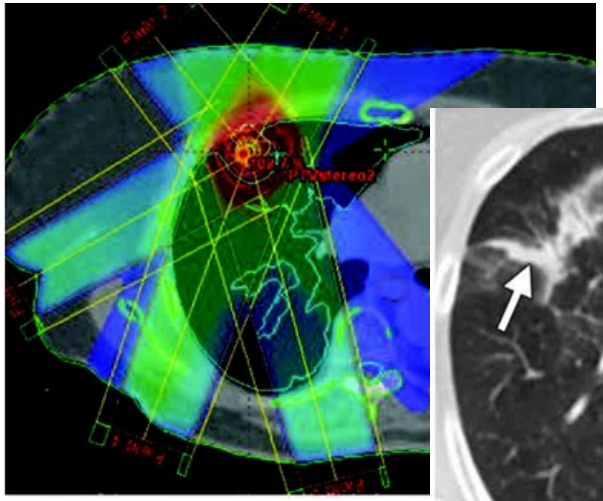
➢ **Diagnosi differenziali:**

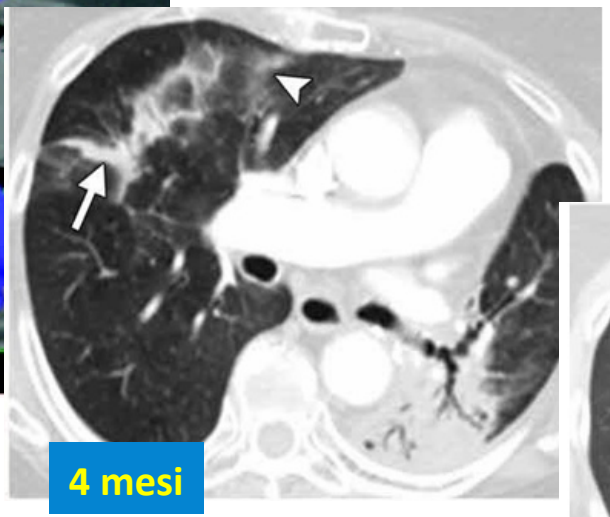
- Infezioni
- Linfangiti carcinomatose
- Neoplasie radioindotte
- **Recidive locali o persistenze di malattia**

CHEST IMAGING

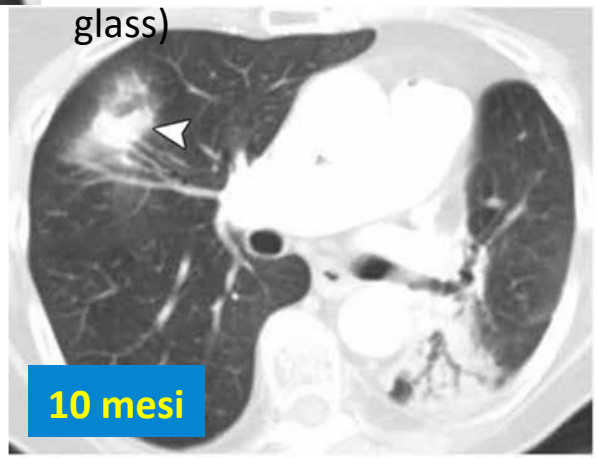
Lung Abnormalities at Multimodality Imaging after Radiation Therapy for Non–Small Cell Lung Cancer 1







consolidazione a chiazze (patchy) e opacità a vetro smerigliato (groud glass)



Non bronchiectasie da trazione

SBRT: Riflessioni

None of these treatment delivery units is superior to the others, with each system clearly having its strengths and weaknesses.
The training and experience of the SBRT team are much more important than the treatment delivery unit used.

Shagal Radiosurgery 2010

CONCLUSIONI

• Da risultati preliminari pubblicati, grazie alla più estensiva prescrizione SBRT, il ruolo della RT nella malattia metastatica si è evoluto dalla palliazione dei sintomi ad un obiettivo potenzialmente curativo

• Nel sottogruppo di pazienti con metastasi solitaria studi investigazionali di dose escalation con SBRT possono essere utili per ottimizzare il controllo locale

• Nei casi con più di una metastasi specialmente se più di un organo è coinvolto I criteri di selezione per SBRT devono essere valutati con attenzione verso l'aspettativa di vita e la tossicità

Thariat et al. Bull Cancer, 2010
Timmerman et al JCO, 2007
Lartigau Et al, Radiat oncol 2012

SBRT : argomenti aperti

- Quale è il reale cut off tra la palliazione pura e l'ipotetico intento curativo nei pazienti oligometastatici

- Quale è il target ottimale e come può il radioterapista definirlo nel migliore dei modi possibili (malattia microscopica)

- Quale è il corretto timing con la cht?.

- Combinazione con I nuovi farmaci e la stereobody

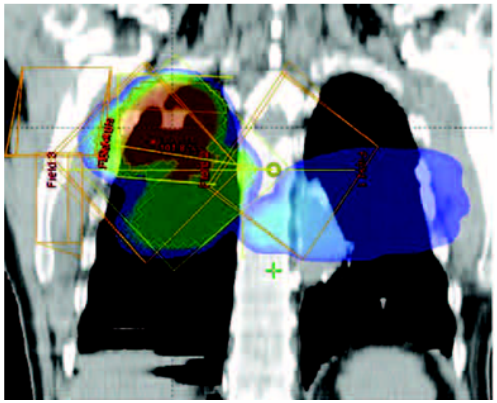
- Validazione del suo ruolo attraverso trials clinici dedicati (dose, outcome)

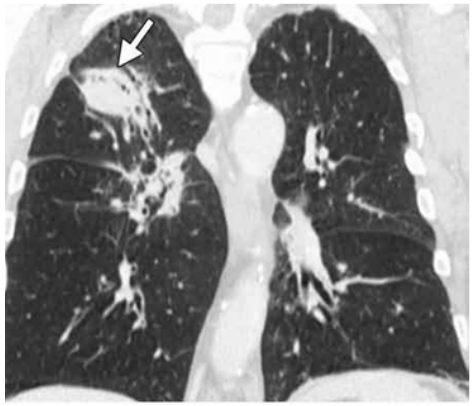
Grazie per l’attenzione

TOSSICITA ’Modificazioni radiologiche tardive

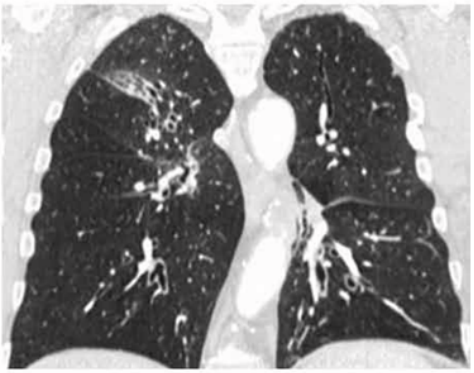
Fibrosi radioindotta

- Modified conventional pattern
- **Mass-like pattern**
- Scar-like pattern





- **Aree di consolidazione arrotondata *2 cm* oltre il tumore**
- **Corrisponde alla zona con più alta dose**
- ***Zone di bronchiectasie da trazione***
- **Può modificarsi la localizzazione nel primo anno di compa con dislocazione verso l’ilo o lontano dall’ilo**



Retrazione della consolidazione

Studio AIRO

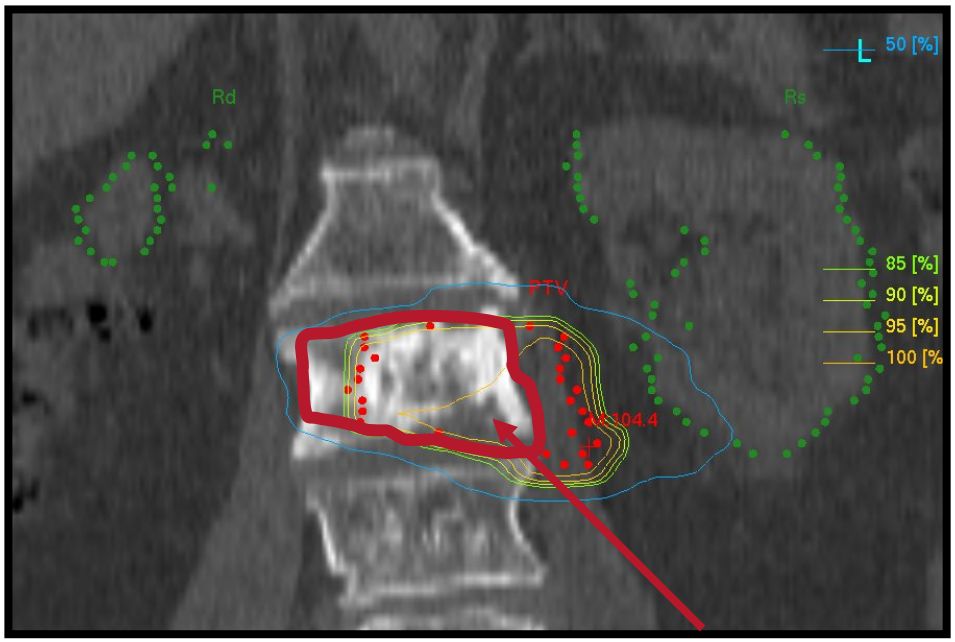
INCLUSION CRITERIA

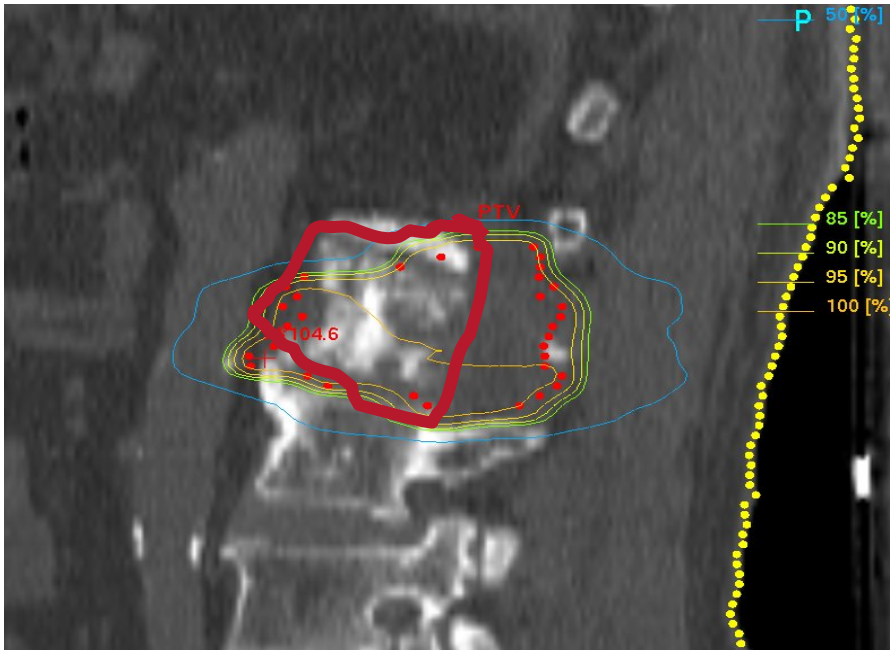
- Inoperable or medically unsuitable for resection
- Maximum tumour diameter < 6cm
- ≤ 3 discrete lesions
- Performance status 0-2
- Good compliance to treatment

	Dose/fraction	Number fractions	Median dose
Standard dose	**25Gy**	**3**	**75 Gy**
Dose reduction 10%	**22.5 Gy**	**3**	**67.5 Gy**
Dose reduction 20%	**20. 63 Gy**	**3**	**61.89 Gy**
Dose reduction 30%	**18.75 Gy**	**3**	**56.25 Gy**

- From February 2010 and September 2011. ***61 patients (74 lesions)***
- Acute toxicity was limited**: 26% G2 transient transaminase elevations definitively returned to baseline**.
- No RILD. No major (grade 4 or 5) late toxicity.
- Median FU: 12 months(2-26)
- ***Actuarial LC at 6, 12 and 22 months were 100%, 94.0%% and 90.6%***
- ***Median OS rate was 19 months***

ASTRO 2012 Annual meeting, Boston





IL VOLUME BERSAGLIO E' PERFETTAMENTE COMPRESO NELL' ISODOSE DI RIFERIMENTO DEL 90%

Dispositivi di immobilizzazione

Table 1

Early Reports on Stereotactic Body Radiotherapy Techniques

Author	Site	Immobilization/ Repositioning	Reported Accuracy	Beam Delivery
Lax et al,1994[3]	Abdomen	Wood frame/stereotactic coordinates on box to skin marks	3.7 mm latitude 5.7 mm longitud	4–8 non-coplanar static beams
Hamilton et al,1995[9]	Spine	Screw fixation of spinous processes to box	2 mm	Arcs with circular collimators
Tokuuye et al,1997[10]	Liver	Prone position/jaw and arm straps	5 mm	Rotational arcs with multileaf collimation
Murphy,1997[8]	Spine	Frameless/implanted fiducial markers with real-time imaging and tracking	1.6 mm radial	Cyberknife
Sato et al,1998[5]	Abdomen	Frameless/combination C x-ray, and linac		Non-coplanar arcs with circular collimators
Lohr et al,1999[11]	Spine	Body cast with stereotact coordinates	≤ 3.6 mm mean vector	4–14 static beams
Wulf et al, 2000[12]	Lung, liver	Elekta body frame	3.3 mm latitude 4.4 mm longitud	5–9 static beams or rotational fields
Nakagawa et al, 2000[6]	Thoracic	Megavoltage CT on linac		Coplanar arc or static beams
Herfarth et al,2001[17]	Liver	Leibinger body frame	1.8–4.4 mm	Coplanar rotation or 6 static beams
Nagata et al, 2002[13]	Lung	Elekta body frame	2 mm	6–10 non-coplanar static beams or 7 dynamic arcs
Fukumoto et al, 2002[18]	Lung	Elekta body frame		8 static beams
Hara et al, 2003[7]	Lung	Custom bed transferred to treatment unit after confirmatory scan	2 mm	> 10 non-coplanar static beams
Hof et al, 2003[14]	Lung	Leibinger body frame	1.8–4 mm	5–6 coplanar static beams
Timmerman et al, 2003[16]	Lung	Elekta body frame	~5 mm	7 non-coplanar static beams

CT = computed tomography; linac = linear accelerator.

Song 2004

TOSSICITA' Polmonite

Polmonite da radiazioni (13-37%) dopo RT 3D
(**V20 o con la MLD (V20 > 30-35%).**

Armstrong 2000 ***Rodrigues 2004***

Se la V20 è<25% minime alterazioni

Graham 1999

Polmonite da radiazioni dopo SBRT (4%) **V_{20} = 3-10%**

Aoki 2004 Trovò 2010

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REPORT

AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY (ASTRO) AND AMERICAN COLLEGE OF RADIOLOGY (ACR) PRACTICE GUIDELINE FOR THE PERFORMANCE OF STEREOTACTIC BODY RADIATION THERAPY

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- strumento educativo per medici
- non sono inflessibili
- non hanno una validità come standard di cura dal punto di vista legale.

- il medico può decidere di cambiare le procedure in base alle

- condizioni cliniche del paziente
- limitazioni delle risorse disponibili
- avanzamenti delle tecnologie e conoscenze.

documentare le decisioni prese.

Aderire a queste linee guida non si associa a una diagnosi accurata e a successo terapeutico.

Fegato

Crioterapia,termoablazione , HIFU sono le alternative ma hanno effettivamente un certo grado di invasività e le indicazioni sono limitate attualmente ***a lesioni piccole e lontano da strutture critiche***

Meijer et al , Ann surg 2009

2009

Multi-Institutional Phase I/II Trial of Stereotactic Body Radiation Therapy for Liver Metastases

Kyle E. Rusthoven, Brian D. Kavanagh, Higinia Cardenes, Volker W. Stieber, Stuart H. Burri, Steven J. Feigenberg, Mark A. Chidel, Thomas J. Pugh, Wilbur Franklin, Madeleine Kane, Laurie E. Gaspar, and Tracey E. Schefter

Phase I/II Trial of SBRT for Liver Metastases

Table 3. Prospective Trials of Stereotactic Body Radiation Therapy for Hepatic Metastases

Study	No. of Lesions	Fractionation	Median Follow-Up	Actuarial Local Control	
				Time	%
Herfarth et al[6]	55	1 × 14 Gy to 1 × 26 Gy	6 months	18 months	67
Hoyer et al[24]	141*	3 × 15 Gy	4.3 years	2 years	79
Milano et al[21]	293†	10 × 5 Gy	41 months‡	2 years	67
Mendez-Romero et al[25]	45	3 × 12.5 Gy§	13 months	2 years	82
Rusthoven et al (this study)	49	3 × 20 Gy	16 months	2 years	92

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Tossicità:

- Transaminasi
- Lieve nausea
- Danni ai tessuti molli:briglie aderenziali con dolore che richiedono videat chirurgico (grado 3 CTCAE) 2%

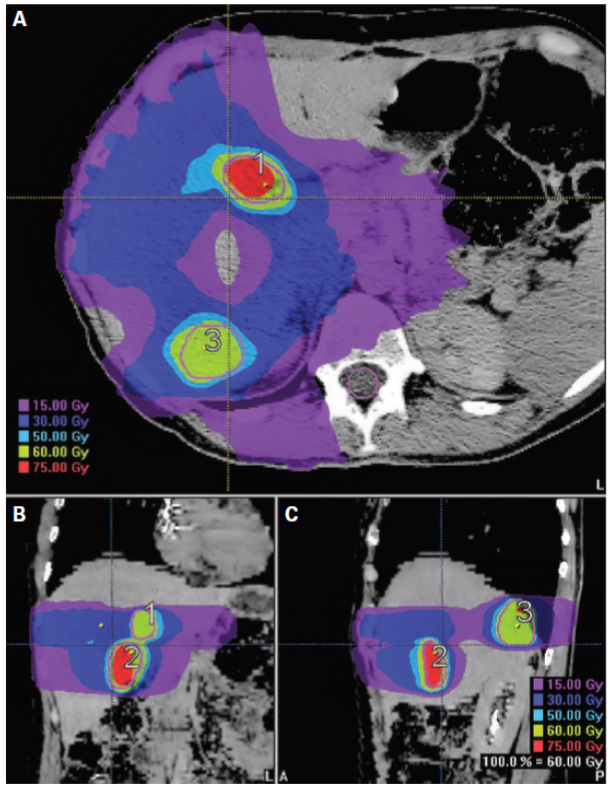

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Table 2. Summary of recent prospective trials with stereotactic body radiation therapy for liver metastases

Study	*n* of patients	Median dose/*n* of fractions	Median follow-up, mos	Local control rate	Overall survival	Toxicity
Herfarth et al. [37, 38]	33	14–26 Gy/1, prescribed to 80%	18	Crude, 78%; 6-mo, 75%; 12-mo, 71%; 18-mo, 67%	1-yr, 72%	Radiation-induced liver disease: 0%
Hoyer et al. [39]	44	45 Gy/3, prescribed to 95%	4.3 yrs	86%	24-mo, 38%	–
Kavanagh et al. [40]	36	60 Gy/3	19	18-mo, 93%	–	–
Lee et al. [42]	70	27.7–60.0 Gy/6, prescribed to isodose line covering PTV (median, 41.4 Gy)	10.8 for 68 assessable patients	1-yr, 71%	18-mo, 47%	Late grade 4 and 5 toxic effects, 2.9% and 1.5%, respectively
Méndez Romero et al. [43]	14	37.5 Gy/3, prescribed to 65%	12.9	Crude, 94%; 1-yr, 100%; 2-yr, 86%	1-yr, 85%; 2-yr, 62%	Grade ≥4 toxic effects, 0%
Rusthoven et al. [44]	47	12–20 Gy/3, prescribed to isodose line covering PTV	16	1-yr, 95%; 2-yr, 92%	2-yr, 30%	Grade 4 toxic effects, 0%
Goodman et al. [45]	26	18–30 Gy/1, prescribed to 80%	17.3	1-yr, 61.8%; 2-yr, 49.4%	1-yr, 61.8%; 2-yr, 49.4%	Late grade 2 gastrointestinal toxic effects, 2 of 26 patients
Rule et al. [46]	27	30–60 Gy/5	20	2-yr, 56%, 89%, and 100% for the 30-Gy, 50-Gy, and 60-Gy cohorts, respectively	–	Grade ≥3 toxic effects, 0%

Abbreviation: PTV, planning target volume.