Associazione Italiana Radioterapia Oncologica

Società Italiana di Radiobiologia

Associazione Italiana Radioterapia Oncologica

Farmaci innovativi e ipofrazionamento

RIMINI 30 settembre- 2 ottobre 2016

La gestione delle tossicità indotte da farmaci innovativi associati alla radioterapia

Anna Merlotti

Radioterapia Oncologica

A.S.O. S.Croce e Carle Cuneo

anna.merlotti@virgilio.it

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DICHIARAZIONE

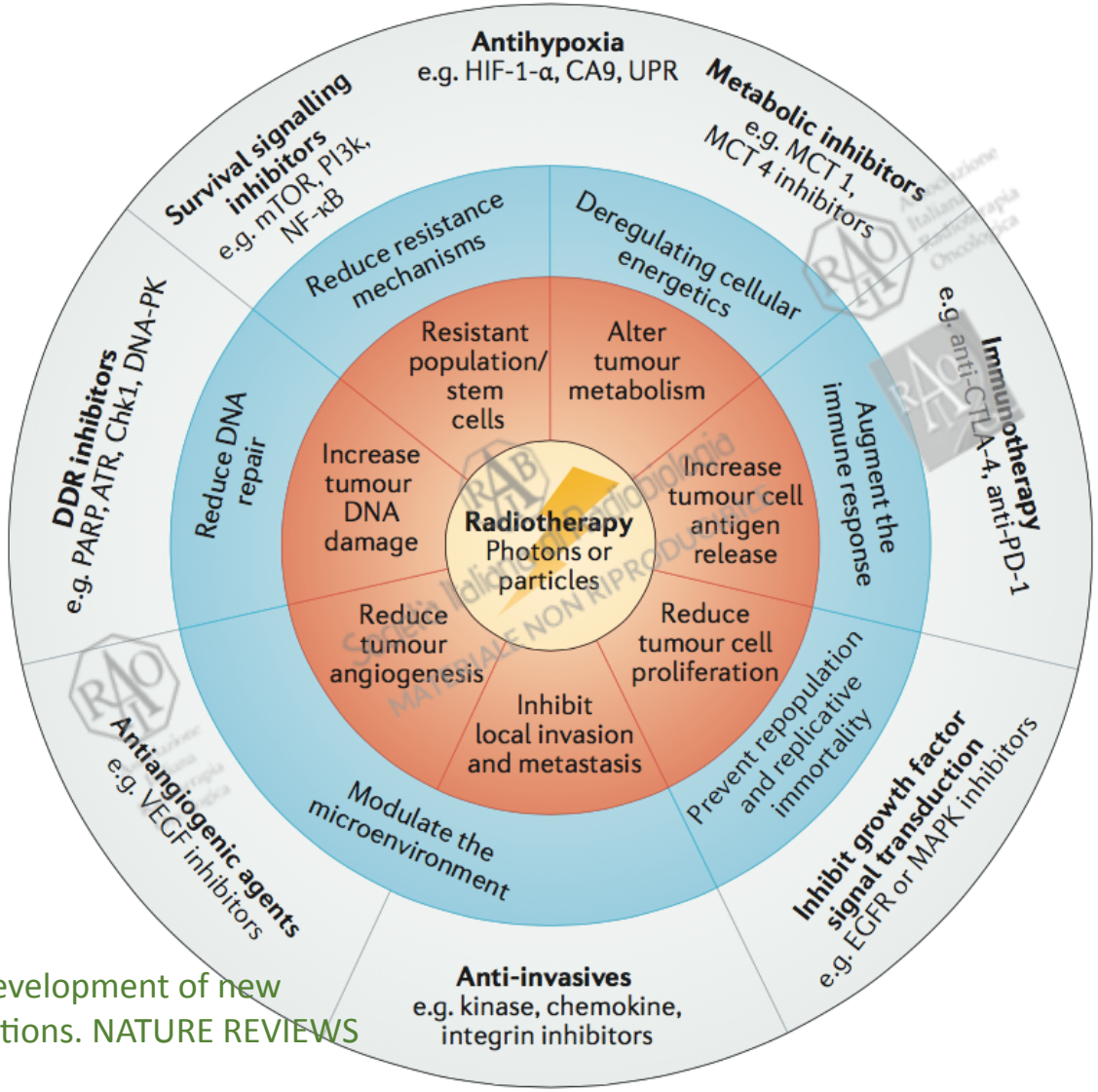
Relatore: Anna Merlotti

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

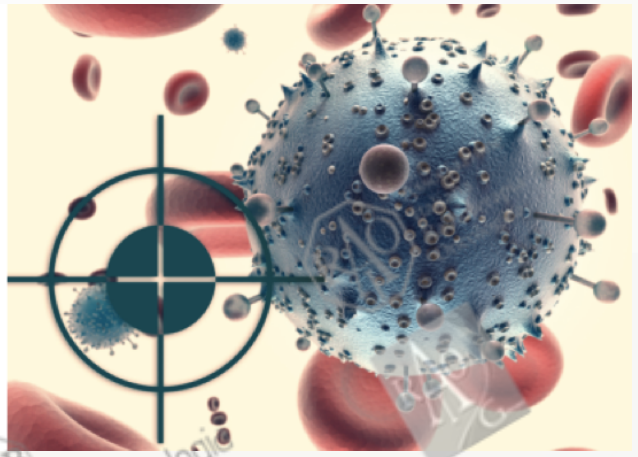
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Innovative drugs

- Therapeutic advance= efficacy, safety, and convenience.
- New drugs are approved on efficacy studies; safety outcomes are a secondary issue.
- Long follow-up on large population (rare and serious effects)



Sharma R.A. et al. Clinical development of new drug–radiotherapy combinations. NATURE REVIEWS CLINICAL ONCOLOGY 2016



- In contrast to conventional anti-cancer treatment which target cellular machinery common to both malignant as well as normal dividing cells, targeted therapy drugs are directed at a more specific target.

- The therapeutic index of RT association with targeted therapies is not necessarily better than that with conventional cytotoxics

- The targets of these therapies may be found in normal tissues and therefore affect multiple organs

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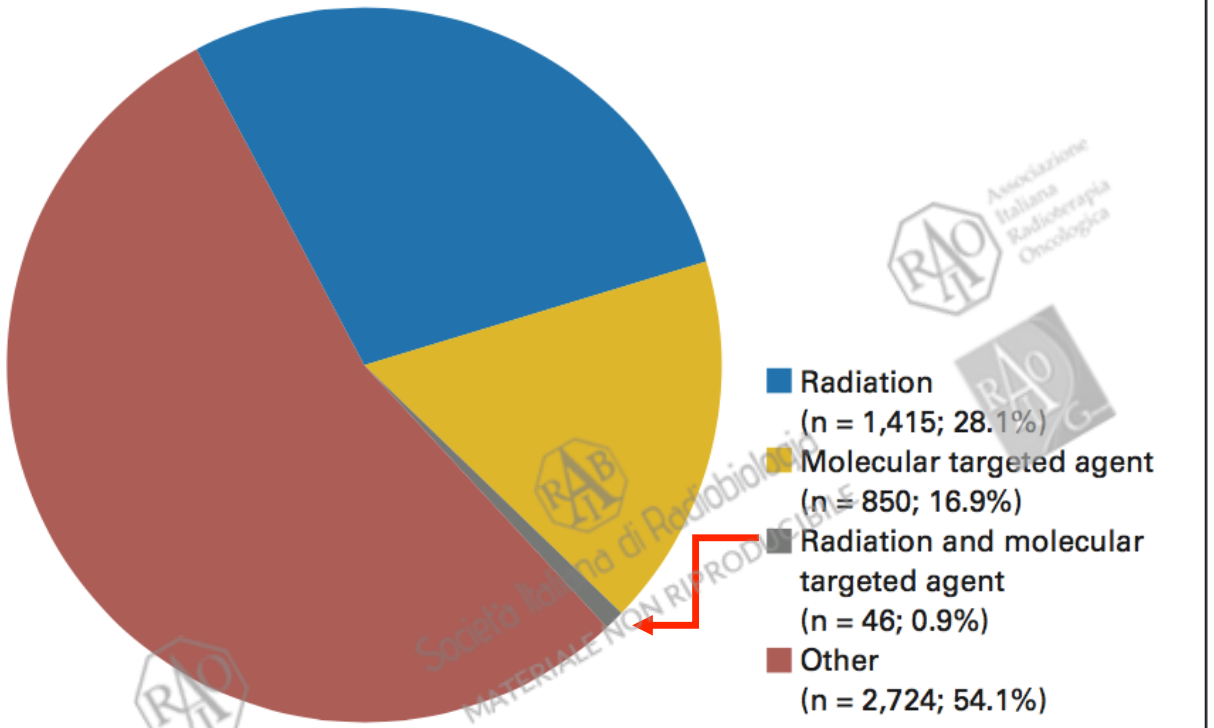

Fig 2. Distribution of current phase III clinical trials in oncology. A search of ClinicalTrials.gov for phase III clinical trials returned 5,035 trials for condition = "cancer." When intervention = "radiation" was added to this search, 1,461 studies were identified. When the 5,035 phase III cancer trials were sorted by intervention, 896 studies involved a molecular targeted agent as defined in this review. Of these, only 46 studies examined a combination of a molecular targeted agent and radiation. Nine studies involving total-body irradiation were excluded from that category.

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Associazioni RT e nuovi farmaci

The main scenarios are

- 1) RT as the main treatment associated with new drugs
- 2) RT given to metastatic patients treated with innovative drugs
- 3) RT used with immune therapies

Associazioni RT e nuovi farmaci

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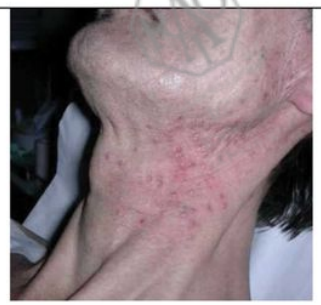
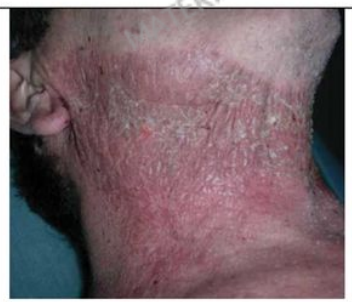
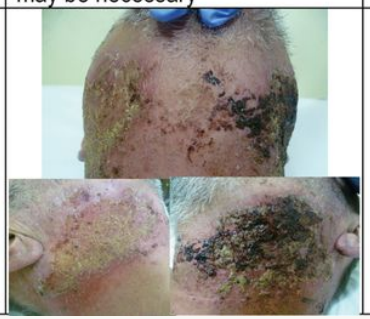
Modello: Cetuximab + RT in SCCHN….anche se

- Although initially defined by the US Food and Drug Administration (FDA) as an agent approved together with a prerequisite diagnostic molecular test, molecular targeted therapies are more broadly defined by their specificity to aberrant cellular processes or molecular characteristics of the tumors they are designed to treat.

- For LAHNSCC, biomarkers for the prediction of an improved response to Cet are lacking.

Proposal of a new grading system for bio-radiation dermatitis.

TERM	G1	G2	G3	G4
Dermatitis Bio-radiation	Faint erythema or dry desquamation; and lesions due to bio-treatment (e.g. xerosis, papules, pustules, and other clinical signs) which may or may not be associated with symptoms of pruritus or tenderness.	Moderate to brisk erythema; patchy moist desquamation in folds and creases; lesions due to bio-treatment (e.g. crusts, papules, pustules, and other clinical signs) mostly confined to less than 50% of radiated area; bleeding lesions with friction or trauma.	Moist desquamation in areas other than skin folds and creases; extensive (>50% of involved field) confluent lesions due to bio-treatment (e.g. crusts, papules, pustules, and other clinical signs) associated to **bleeding by minor trauma or abrasion**.	Life-threatening consequences: skin necrosis or ulceration of full thickness dermis; extensive (>50% of involved field) confluent lesions due to bio-treatment (e.g. crusts, papules, pustules, and other clinical signs) associated to signs of **spontaneous bleeding**. Systemic inflammation response syndrome (SIRS)
Activity of Daily living (ADL)	No limiting age-appropriate ADL	Limiting age-appropriate instrumental ADL.	Limiting self care ADL	
Action	Topical therapy indicated (moisturizers, corticosteroids, antibiotics)	Topical and oral therapy indicated	Topical and oral therapy indicated; dressing and wound care indicated; inpatient therapy may be necessary	
				

E. G. Russi et al. Ann Oncol 2013;24:2463-2465

Annals of Oncology

Cardiotossicità Trastuzumab: perché?

- Il recettore HER2 è importante nello sviluppo cardiaco
- Stress cardiaco (antracicline): incremento dell'espressione dei recettori HER2 ed un incremento del legame tra neuroreguline (NRG-1) e HER2.
- Il legame NRG-1 e HER2 attiva una via di sopravvivenza importante.
- Trastuzumab compete con NRG-1 e inibisce la sopravvivenza della cellula miocardica

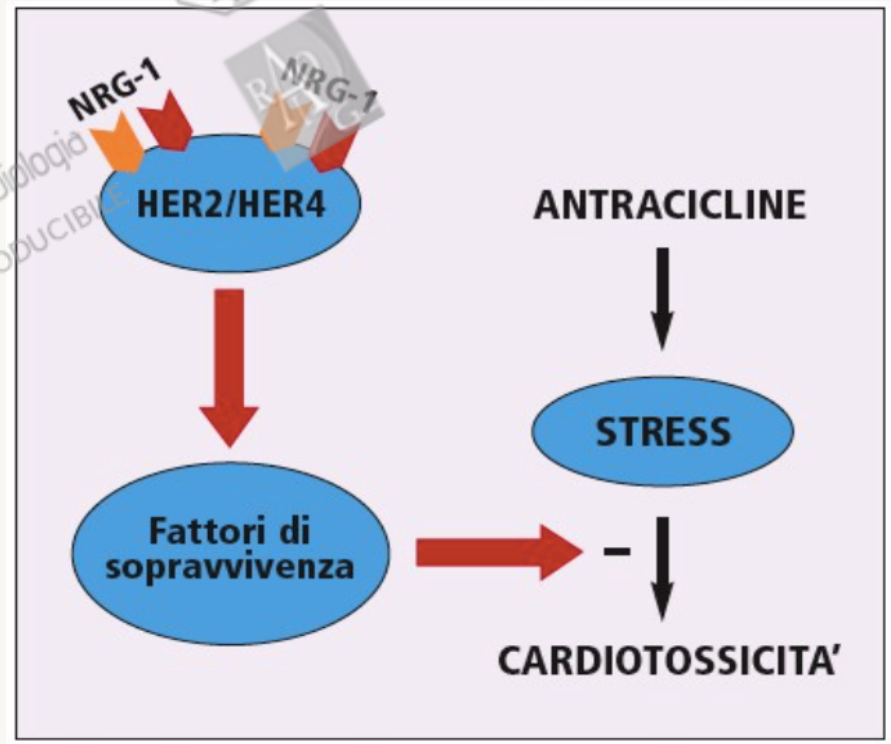


Figura 1. Ruolo del legame NGR-1/HER2 come meccanismo di difesa nel cuore sottoposto a stress indotto da antracicline.

DE GRUYTER OPEN

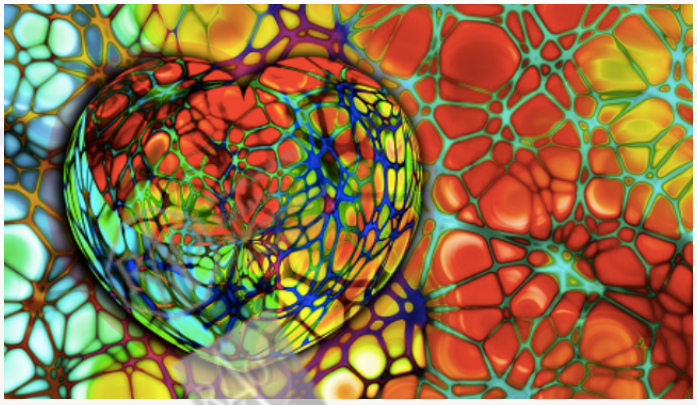
Radiology and Oncology

This Article This Journal Submit a manuscript

Radiol Oncol. 2014 Jun; 48(2): 105–112. PMCID: PMC4078028
Published online 2014 Apr 25. doi: 10.2478/raon-2013-0040

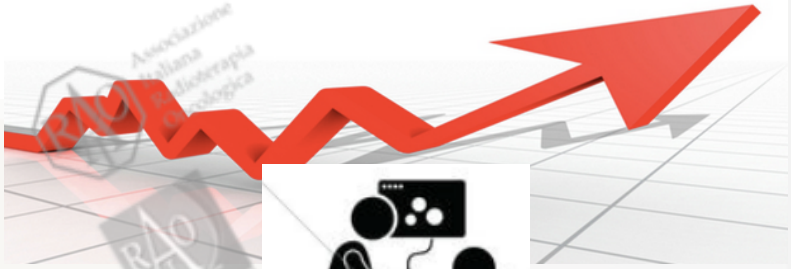
Cardiotoxicity of concomitant radiotherapy and trastuzumab for early breast cancer

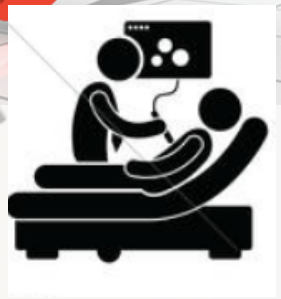
Tanja Marinko,[1] Jure Dolenc,[2] and Cvetka Bilban-Jakopin[3]



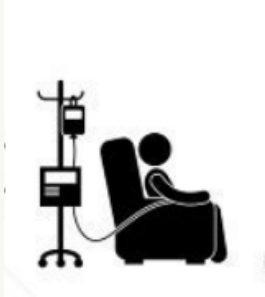
- Radiation upregulates HER2/neu gene expression in human breast cancer cell lines (> response to trastuzumab), not yet clear whether it radiosensibilizes cells of healthy tissues too.
- radiation damage: microvascular lesions. Final outcome is fibrosis (years).
- At present no increased cardiac toxicity. However, follow-up periods only estimate early cardiac toxicity caused by trastuzumab.
- New HER2 inhibitors (lapatinib, pertuzumab) have been used alone or in combination with trastuzumab, the question of co-toxicity of trastuzumab and radiation is even more important.

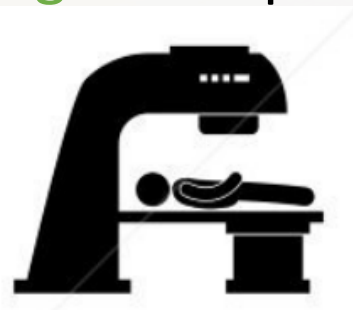
Gestione tox: multidisciplinarietà + dati a lungo termine





- Goal: to dicover dysfuncion early
- Diastolic disfunction may be better predictor
- Diagnostic testing: ECO-D, monitor every 3 months
- Blood testing: Troponina I= heart injury, Type-B natriuretic peptide (BNP).
- Guidelines for management of TIC are still lacking. Enalapril (ACE-inhibitor), carvedilol (beta-blocker)
- Withdrow Trastuzumab
- Dosimetric correlations





Associazioni RT e nuovi farmaci

The main scenarios are

- 1) RT as the main treatment associated with new drugs

- **2) RT given to metastatic patients treated with innovative drugs**

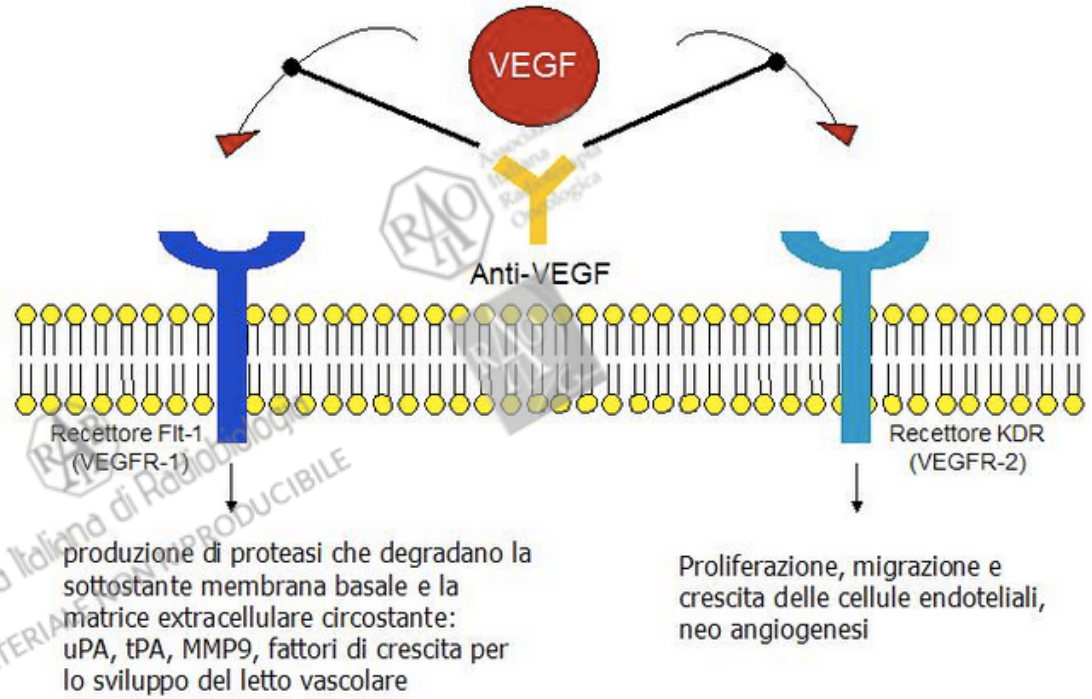
- 3) RT used with immune therapies

II difficoltà:

- diverse dosi e tecniche di RT:
  SRT vs CRT (our understanding of normal organ tolerance with SBRT is still in its infancy).
- uso cronico: grade 2 tox bearable for a short period, **impair QoI and can reduce RT tolerability when chronic**

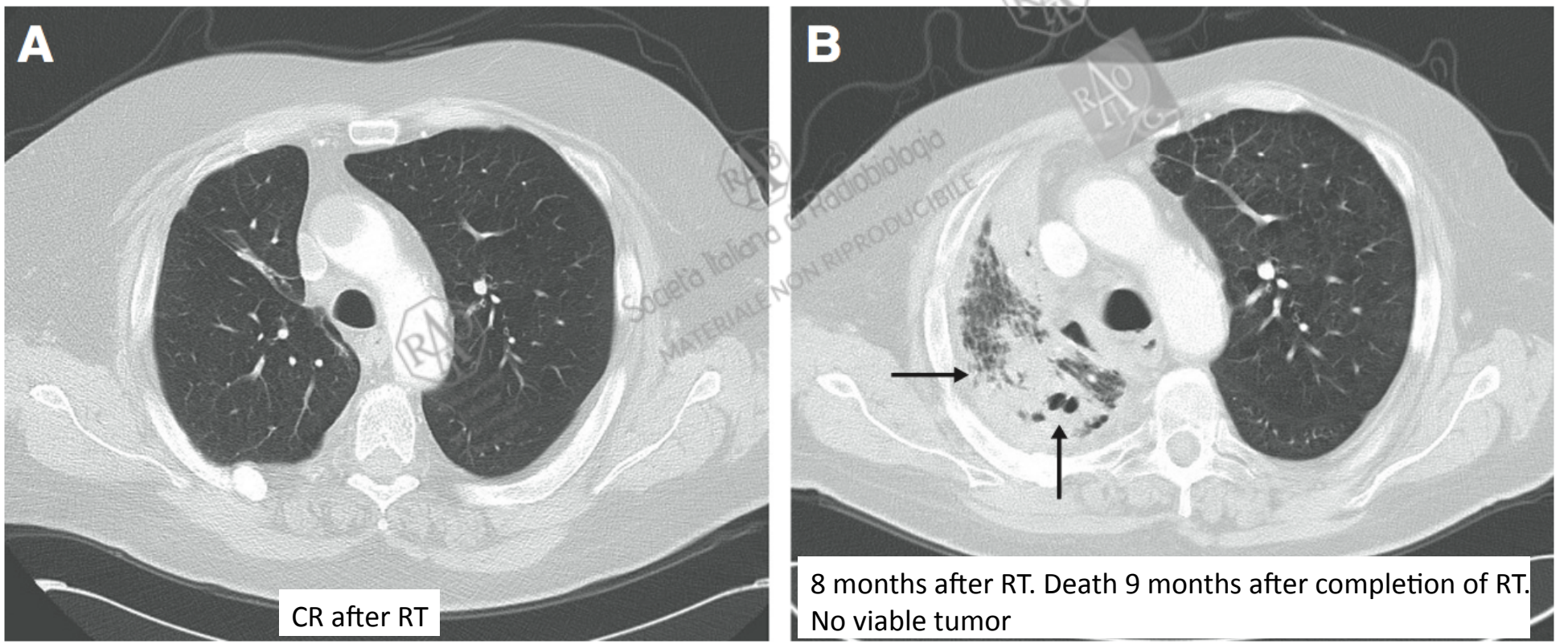
Bevacizumab

- side effects of bevacizumab alone include
  - impaired wound healing,
  - hypertension,
  - bleeding problems
  - increased risk of thromboembolic events.
- Half-life: 20 d (range 15-50)

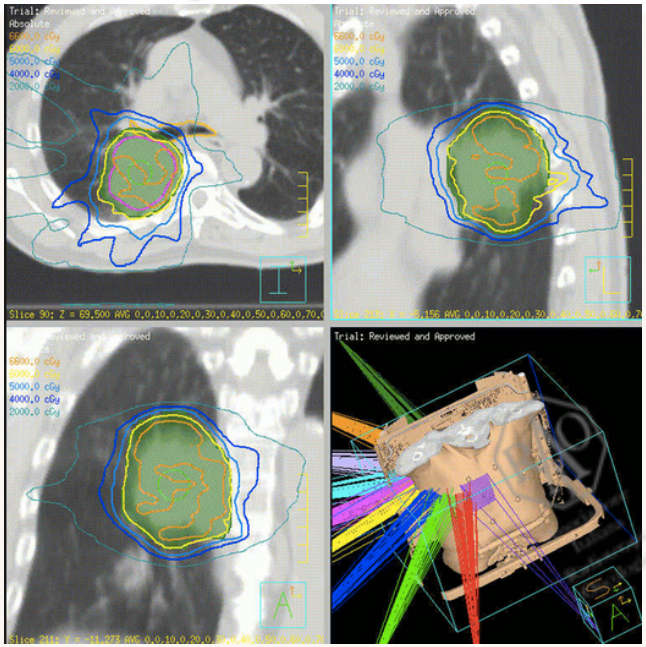


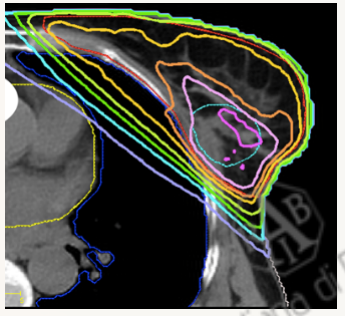
- Hypertension and proteinuria caused by phenomena of vasoconstriction , vascular endothelial dysfunction and depletion.
- bevacizumab forms an immune complex with VEGF and induces platelet aggregation and degranulation, which may be the mechanism of bevacizumab-associated thrombosis

Pulmonary Toxicity After Bevacizumab and Concurrent Thoracic Radiotherapy Observed in a Phase I Study for Inoperable Stage III Non–Small-Cell Lung Cancer



BJR Late toxicities and outcomes of adjuvant radiotherapy combined with concurrent bevacizumab in patients with triple-negative non-metastatic breast cancer





Dose/volume

Late toxicities	Bevacizumab + RT, *n* (%)		RT alo	
Late toxicities evaluation				
Yes	38 (97%)		9%)	
No	1 (3%		5 (11%)	
	Grad	3–4	Grades 1–2	Grades 3–4
Pain		0	6 (15%)	0
Fibrosis		0	2 (5%)	0
Telangiect	(5%)	0	0	0
Arr	3 (8%)	0	2 (5%)	0
	0	0	0	0
ial ischaemia	0	0	0	0
icarditis	0	0	0	0
Dyspnoea	1 (3%)	0	0	0
Dysphagia	0	0	0	0
Paresis	0	0	2 (5%)	0

Non enhanced pulmonary tox.

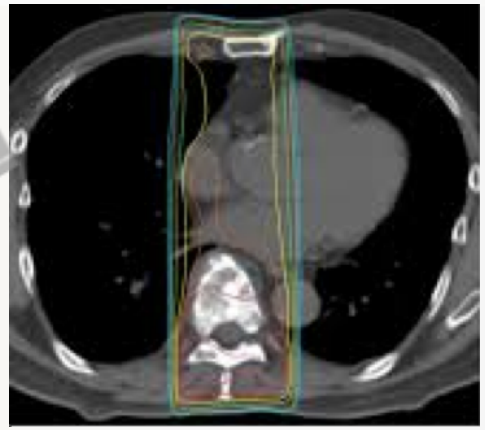
Pernin V, Br J Radiol. April 2015; 88(1048).

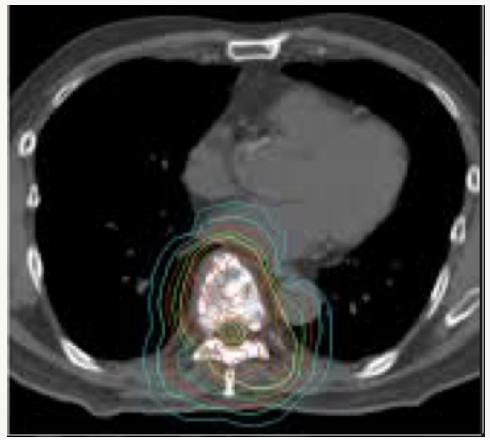
Anticancer Drugs. 2015 Apr;26(4):443-7. doi: 10.1097/CAD.0000000000000204.

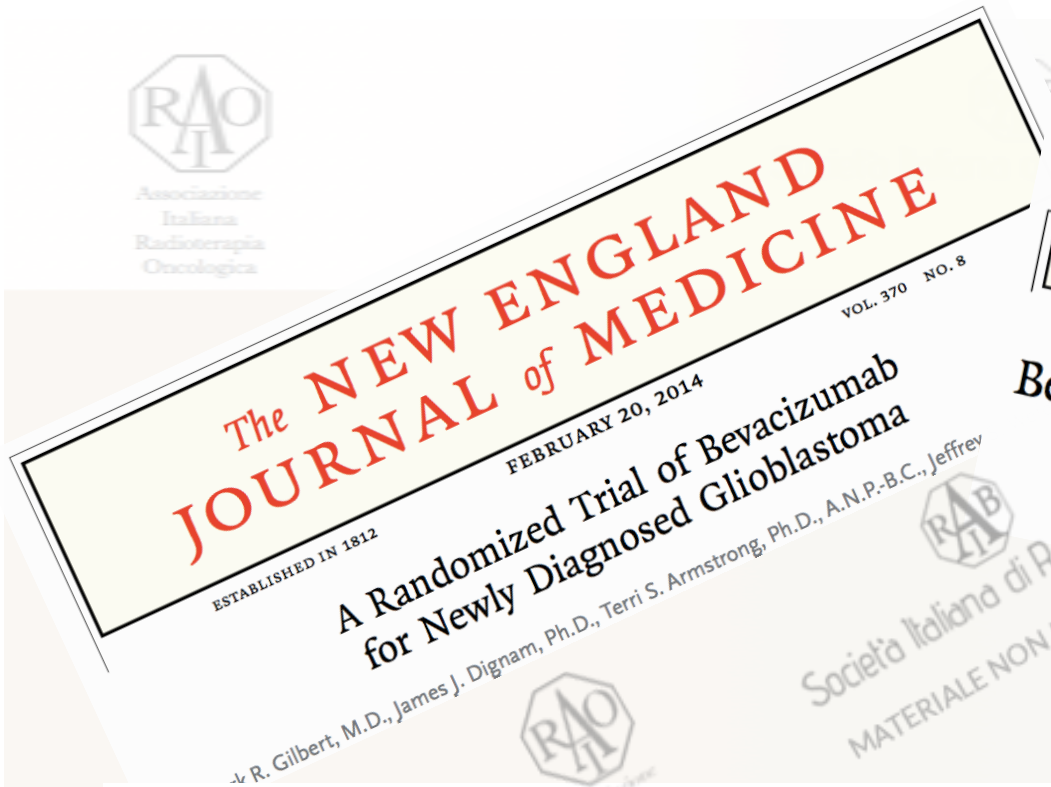
Safety of spinal radiotherapy in metastatic cancer patients receiving bevacizumab therapy: a bi-institutional case series.

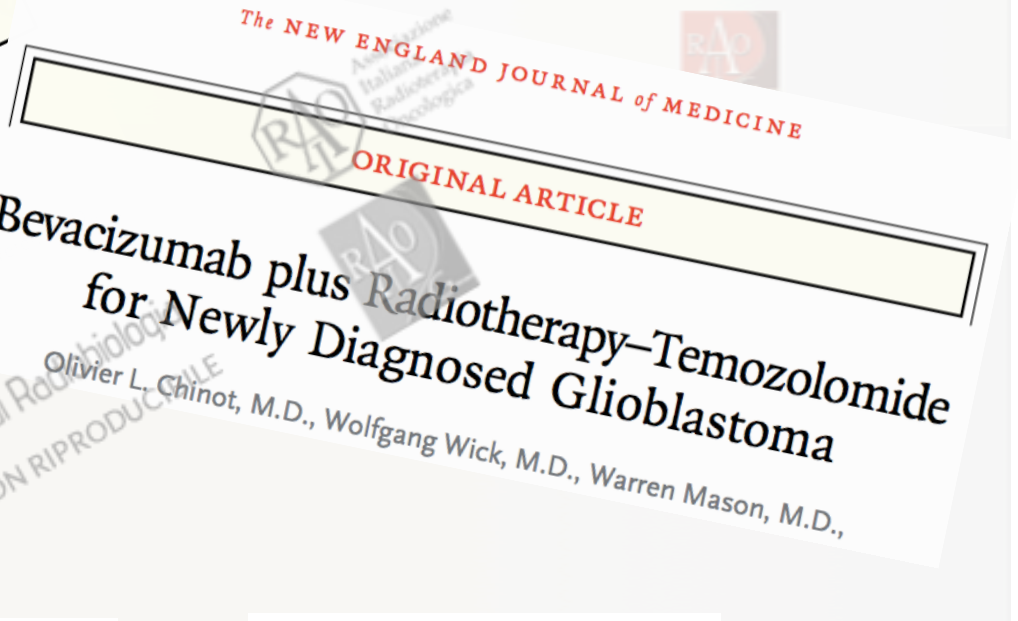
Mbagui R[1], Langrand-Escure J, Annede P, Mery B, Ceccaldi B, Guy JB, Falk AT, Bauduceau O, Bosacki C, Jacob J, Helissey C,

- 18 pts. In 10 pts (56%), irradiation to the thoracic vertebrae.
- RT was delivered at doses of 30 Gy in 10 fx (n=8), 20 Gy in 5 fx (n=9) or 18 Gy in 9 fx (n=1).
- All toxicities were mild to moderate.
- No acute toxicity reported in 13 patients (72%).
- No delayed toxicity was reported within RT fields among 11 patients with at least 6 months of follow-up.









RTOG 0825 637 pts: Neurocognitive decline, increased symptom severity, and decline in health-related quality of life were found over time among patients who were treated with bevacizumab.

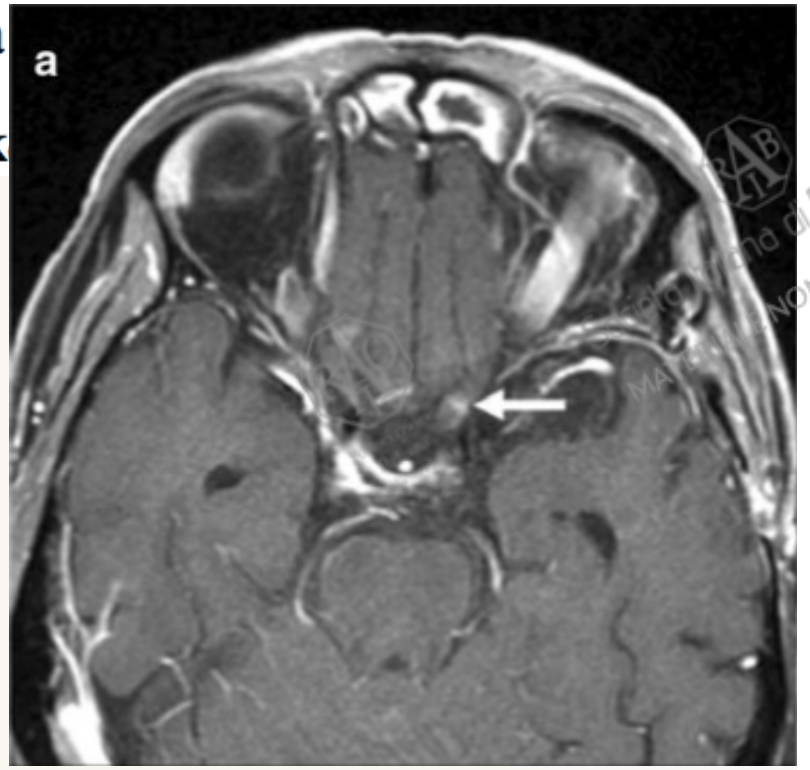
AVAglio 921 pts: maintainance of QoL

J Neurooncol (2011) 102:485–490
DOI 10.1007/s11060-010-0336-0

CASE REPORT

Unexpected late radiation neurotoxicity following bevacizumab use: a

Paul J. K



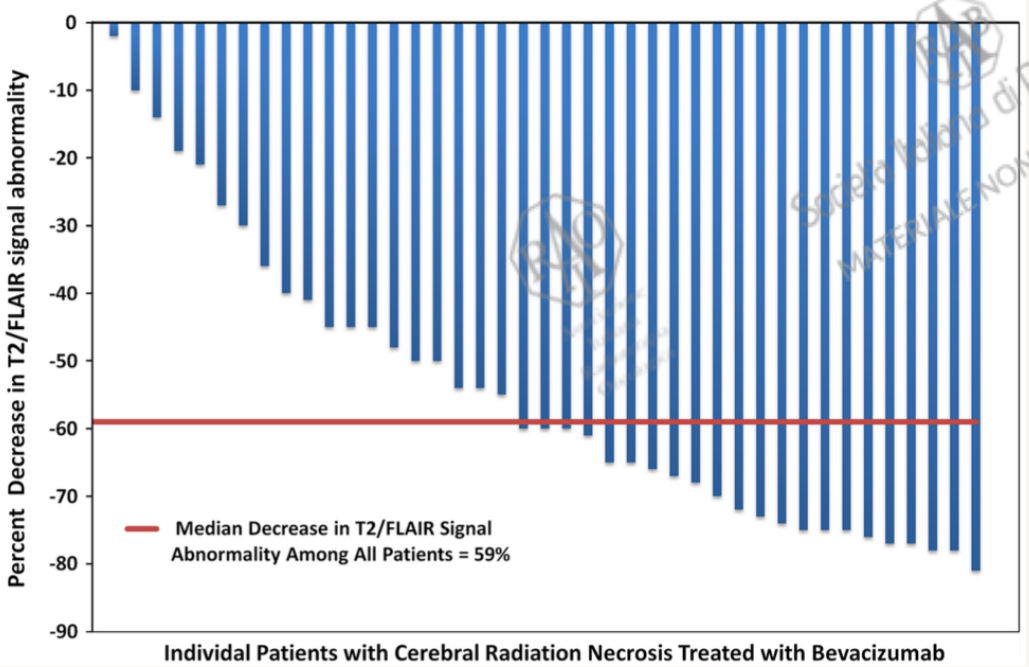
- In five of the six cases bevacizumab was administered at progression.
- Interaction between radiation and bevacizumab appears not to be temporally related to the concomitant administration

J Neurooncol (2014) 117:321–327
DOI 10.1007/s11060-014-1391-8

CLINICAL STUDY

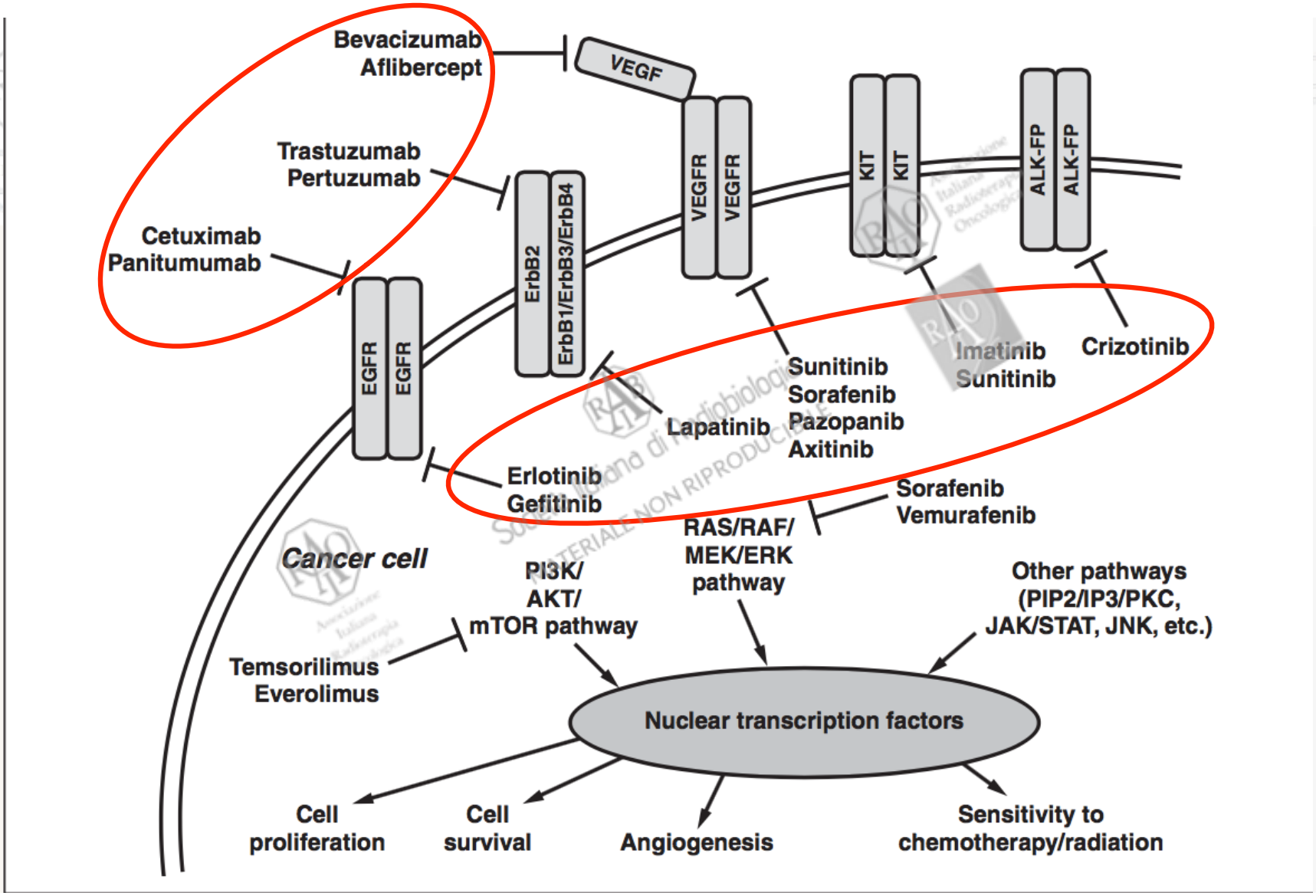
An analysis of radiation necrosis of the central nervous system treated with bevacizumab

Karen Tye · Herbert H. Engelhard · Konstantin V. Slavin · M. Kelly Nicholas ·

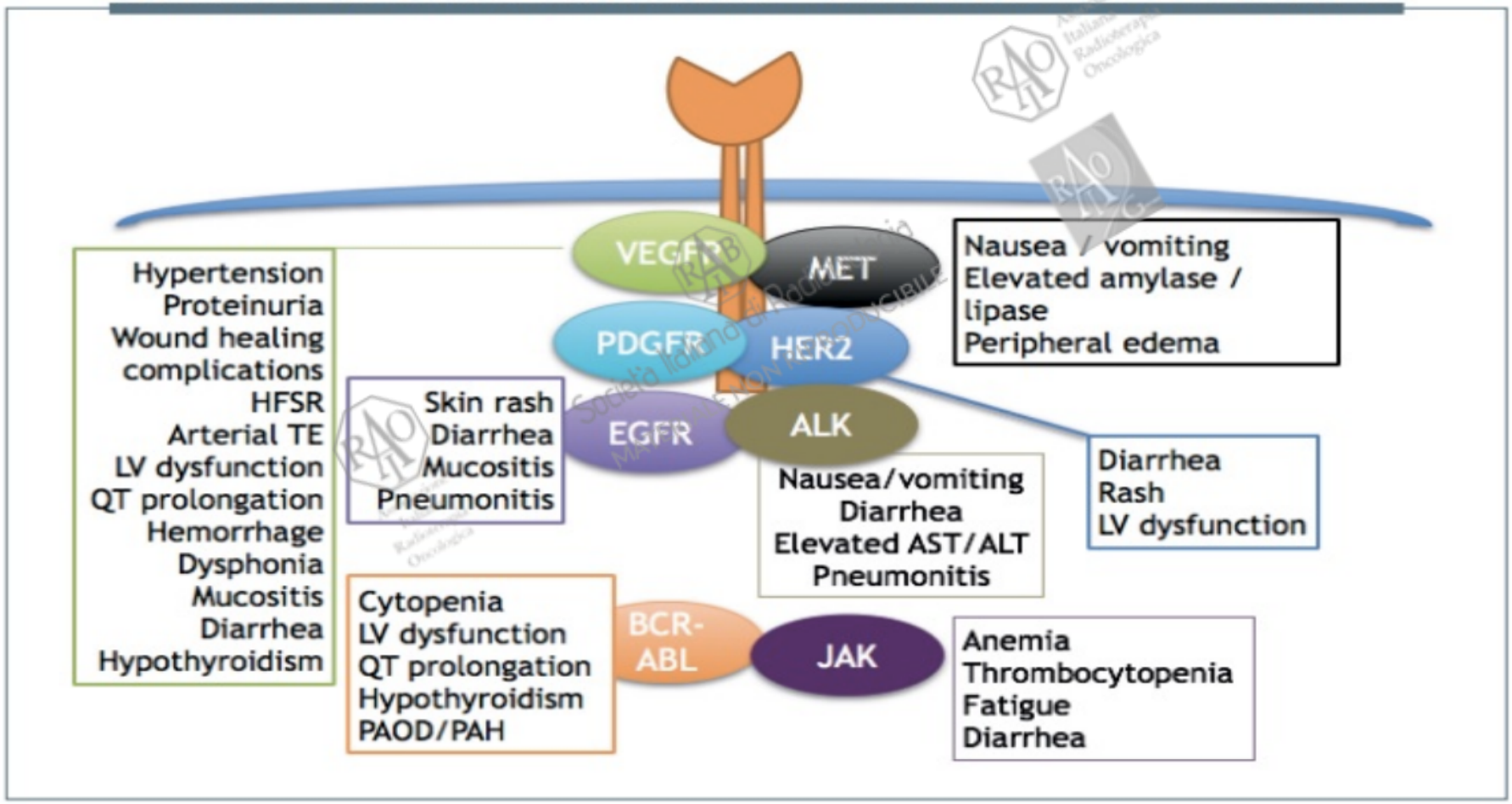


- The vascular supply within the brain parenchyma is maintained by a balance of proangiogenic and antiangiogenic molecules

- The prolonged use of bevacizumab disrupt this balance and can lead to inadequate tissue perfusion and worsening necrosis, which was reported in one patient in this series

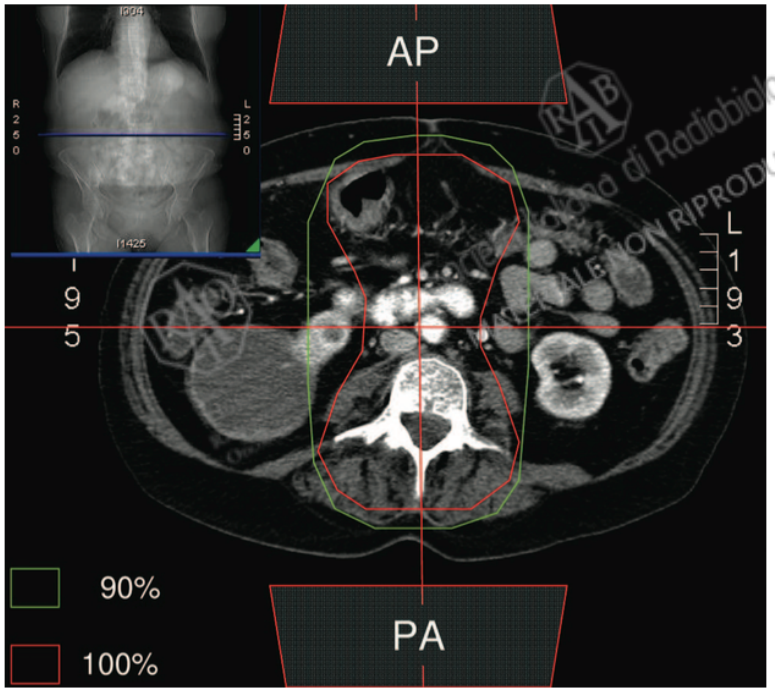
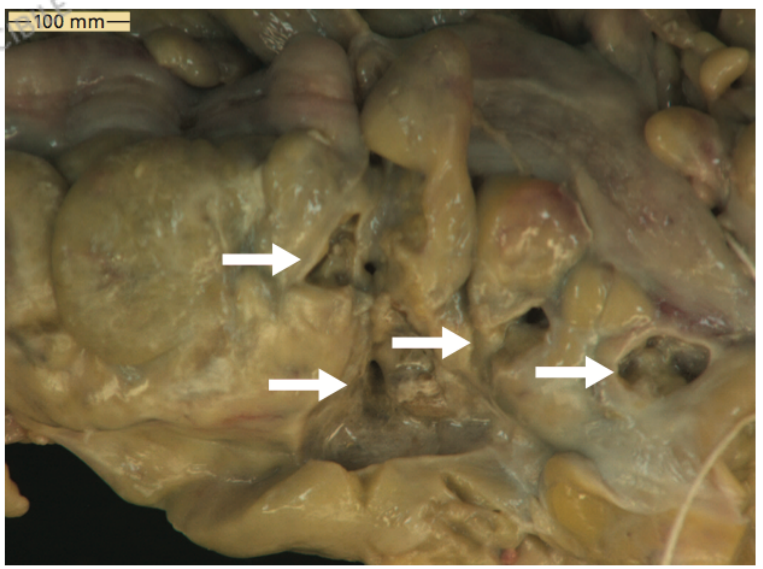

Bevacizumab
Aflibercept
VEGF
Trastuzumab
Pertuzumab
Cetuximab
Panitumumab
ErbB2
ErbB1/ErbB3/ErbB4
VEGFR
VEGFR
KIT
KIT
ALK-FP
ALK-FP
EGFR
EGFR
Lapatinib
Sunitinib
Sorafenib
Pazopanib
Axitinib
Imatinib
Sunitinib
Crizotinib
Erlotinib
Gefitinib
Sorafenib
Vemurafenib
RAS/RAF/
MEK/ERK
pathway
Cancer cell
PI3K/
AKT/
mTOR pathway
Other pathways
(PIP2/IP3/PKC,
JAK/STAT, JNK, etc.)
Temsorilimus
Everolimus
Nuclear transcription factors
Cell
proliferation
Cell
survival
Angiogenesis
Sensitivity to
chemotherapy/radiation

OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS



GI tox: Combined Antiangiogenic and RT

Pollom EL et al. Int J Radiat Oncol Biol Phys. 2015 July 1; 92(3): 568–576

Peters NAJC JCO 2(		al mts	Died peritonitis (multiple necrosis colon in field)
Lordick F IJROBP 2(			
Barney BM IJROBP			
Stephans KL IJROBI			

Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases

Kao J et al. Target Oncolol 2014

Phase I/II trial. 25 pts. Concurrent sunitinib and radiation (50 Gy 10 fx)

- Acute grade ≥3 toxicities was 33%, most commonly myelosuppression, bleeding and abnormal liver function tests.
- 4 % G5 tox, gastrointestinal hemorrhage (out-field), 1 fatal hemoptysis re-RT
- RT to large volumes of bone marrow and liver can exacerbate hematological toxicities associated with sunitinib.
- When concurrent with RT, a reduced daily dose of 37.5 mg is recommended.
- extreme caution in patients with a history of non-inducible bleeding and patients requiring anticoagulation.

Phase 2 Study of Combined Sorafenib and Radiation Therapy in Patients With Advanced Hepatocellular Carcinoma

Adverse event	Grade 0-1	Grade 2	Grade 3	Grade
Adverse side effects during sequential use of sorafenib (n=36)				
Hand and foot skin reaction	32 (88.9%)	4 (11.1%)	0	0
Diarrhea	34 (94.4%)	2 (5.6%)	0	0
Hepatic toxicities	19 (52.8%)	8 (22.2%)	5 (13.9%)	4 (11.1%)
Gastric or duodenal ulcer	33 (91.6%)	2 (5.6%)	1 (2.8%)	0
Hepatic toxicities	26 (65%)	10 (25%)	4 (10%)	0

Effetto sinergico?

Animal studies have shown dose dependent increased expression of transforming growth factor-beta 1 (TGF-ß1) in the liver of irradiated rats which may be an important factor in the development of RILD in humans.

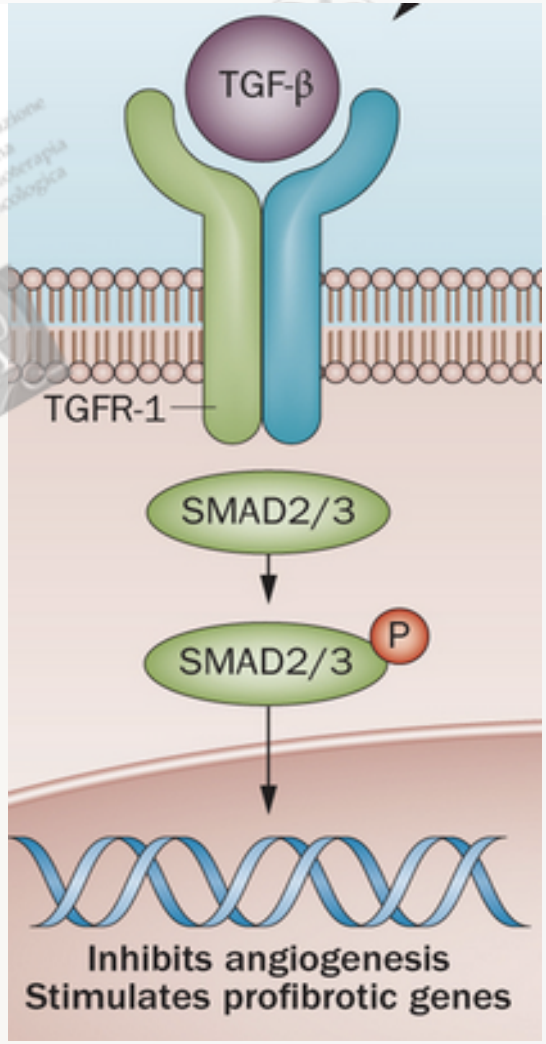
Still true?

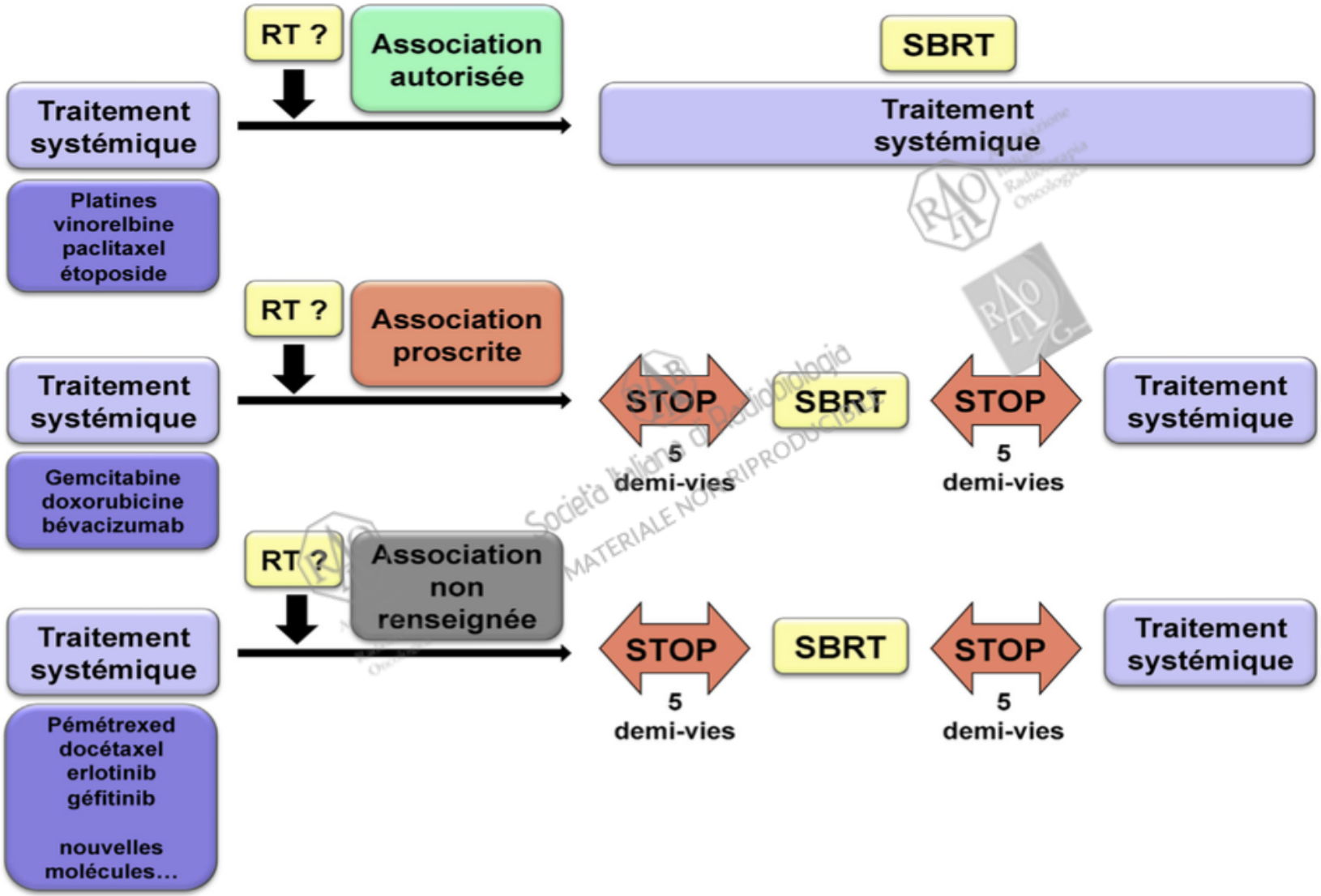
Mean dose should be kept below 28 Gy and 32 Gy in conventional fractionation for primary HCC and liver metastases respectively.

The volume of liver receiving 30 Gy should be less than 60% of the liver volume.

The mean dose must be kept less than 13–18 Gy for three fractions and less than 15–20 Gy for six fractions SBRT.

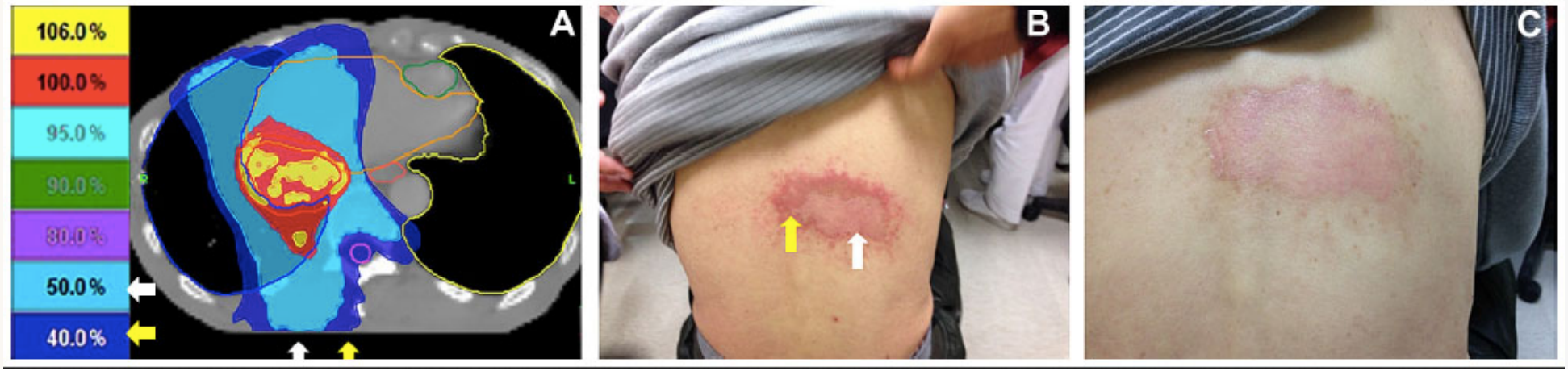
V15 Gy to less than 700 mL in three to five fractions SBRT.

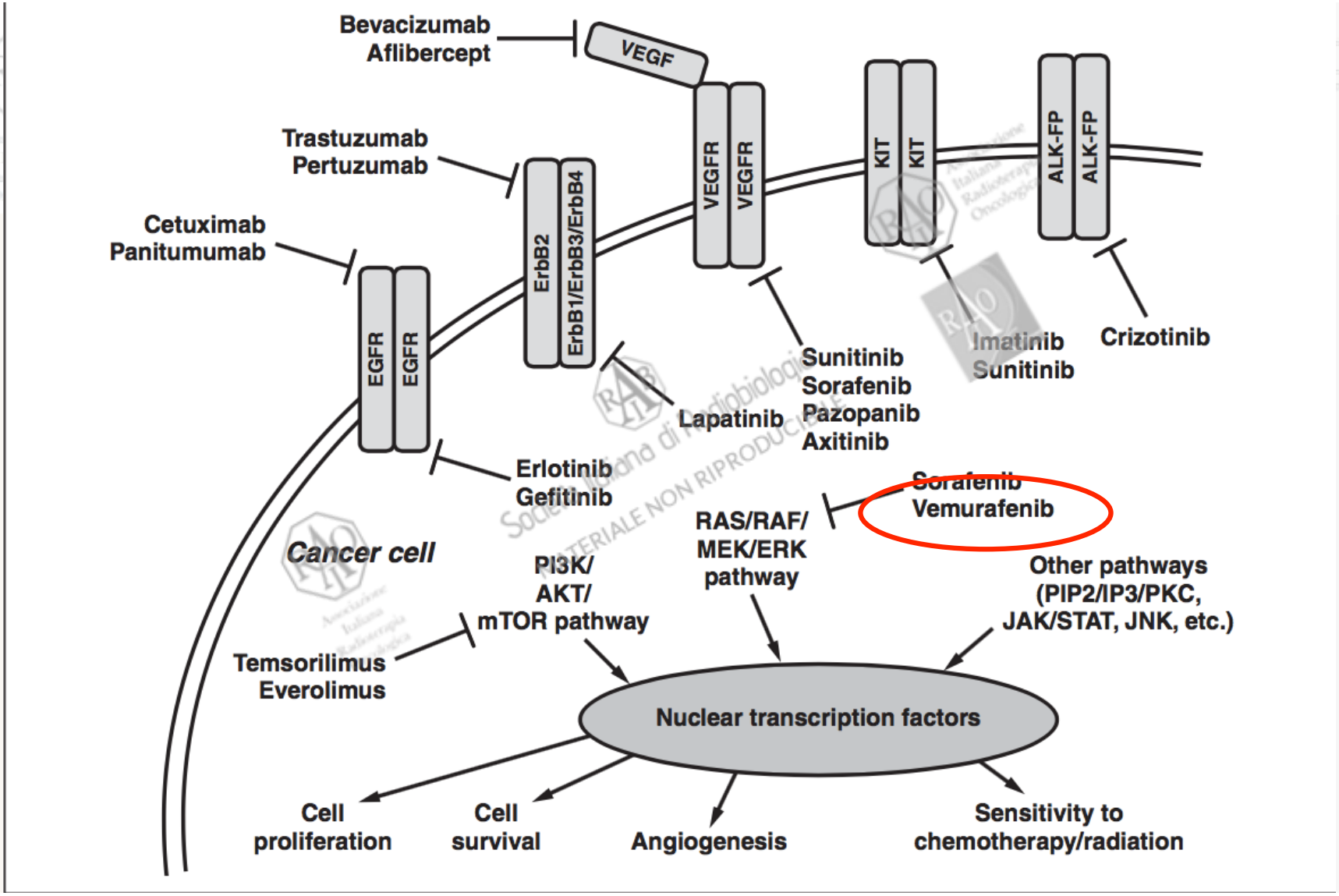



RT ?
Association autorisée
SBRT
Traitement systémique
Traitement systémique
Platines
vinorelbine
paclitaxel
étoposide
RT ?
Association proscrite
Traitement systémique
STOP
5 demi-vies
SBRT
STOP
5 demi-vies
Traitement systémique
Gemcitabine
doxorubicine
bévacizumab
RT ?
Association non renseignée
Traitement systémique
STOP
5 demi-vies
SBRT
STOP
5 demi-vies
Traitement systémique
Pémétrexed
docétaxel
erlotinib
géfitinib
nouvelles molécules…

Radiation recall?

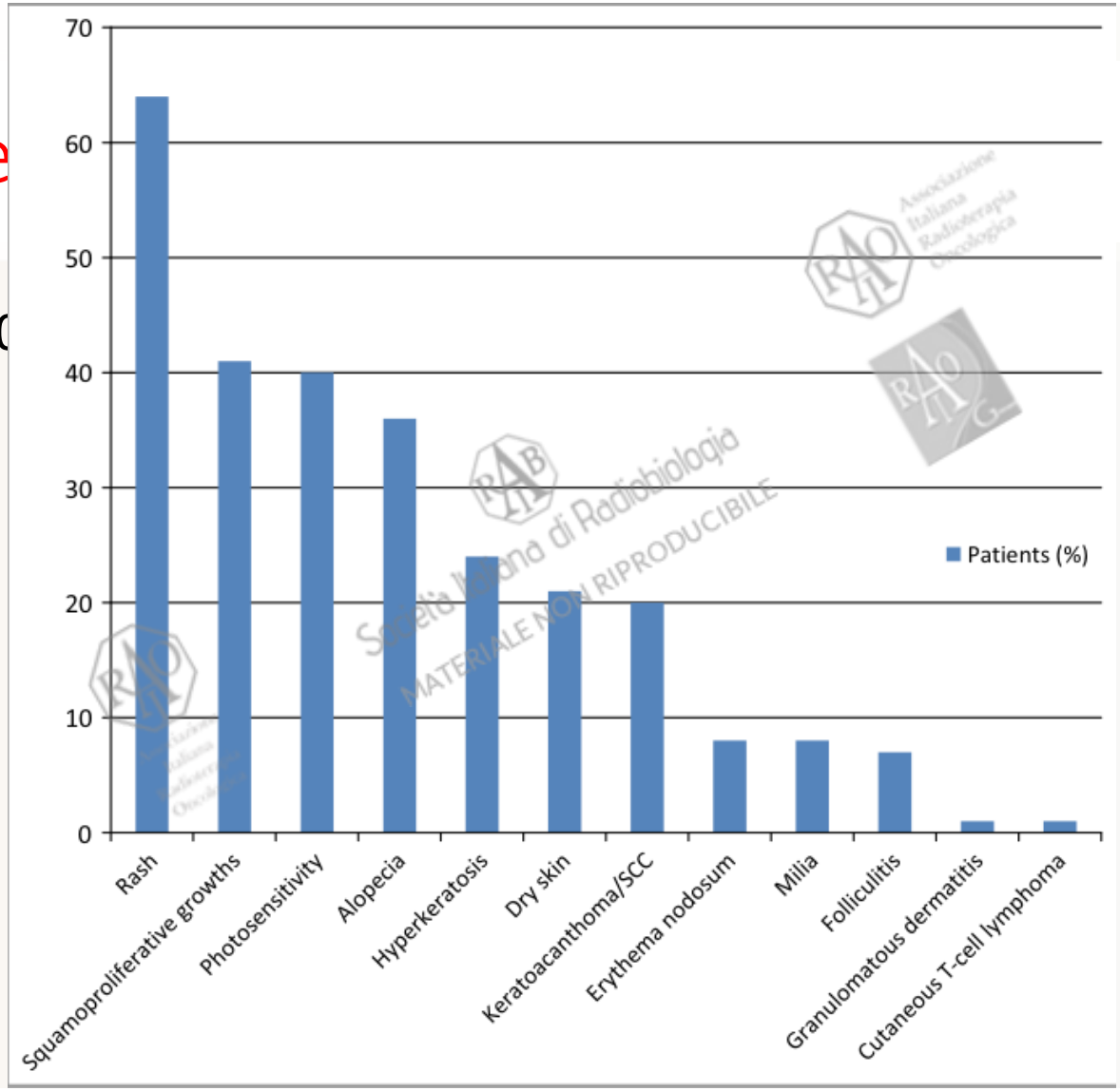
- Radiation recall is known as chemotherapy-triggered inflammatory reaction in previously exposed areas to irradiation but the mechanism is poorly understood.
- Radiation recall dermatitis 8%, multiple drugs. Pathogenesis unknown
- Pneumonitis, myositis, mucositis…

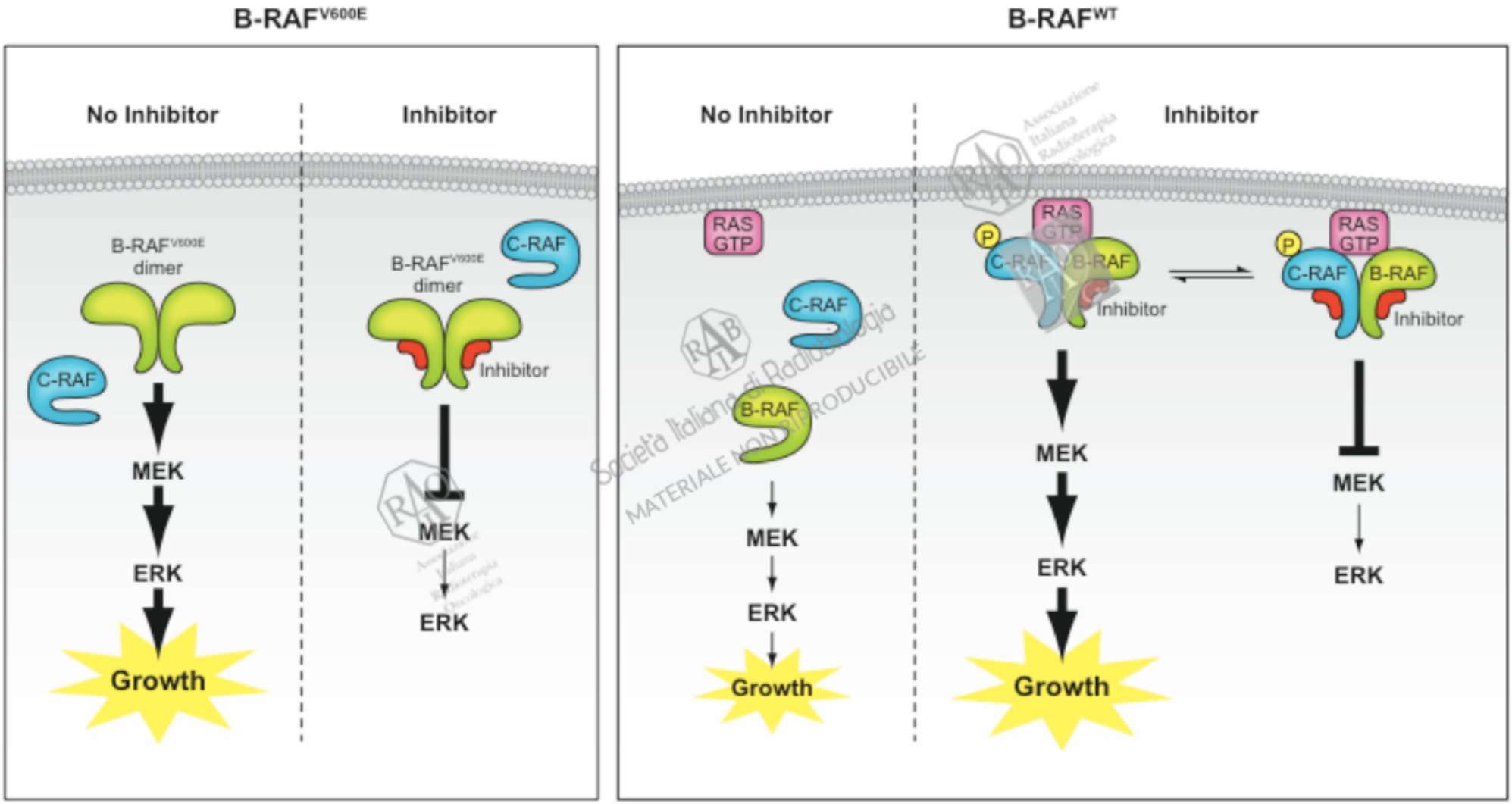



Bevacizumab
Aflibercept
VEGF
Trastuzumab
Pertuzumab
ErbB2
ErbB1/ErbB3/ErbB4
VEGFR
VEGFR
KIT
KIT
ALK-FP
ALK-FP
Cetuximab
Panitumumab
EGFR
EGFR
Lapatinib
Sunitinib
Sorafenib
Pazopanib
Axitinib
Imatinib
Sunitinib
Crizotinib
Erlotinib
Gefitinib
Sorafenib
Vemurafenib
RAS/RAF/
MEK/ERK
pathway
Cancer cell
PI3K/
AKT/
mTOR pathway
Other pathways
(PIP2/IP3/PKC,
JAK/STAT, JNK, etc.)
Temsorilimus
Everolimus
Nuclear transcription factors
Cell
proliferation
Cell
survival
Angiogenesis
Sensitivity to
chemotherapy/radiation

Ve

- BRAF V600




B-RAF^V600E
No Inhibitor
Inhibitor
B-RAF^V600E dimer
C-RAF
MEK
ERK
Growth
B-RAF^V600E dimer
C-RAF
Inhibitor
MEK
ERK
B-RAF^WT
No Inhibitor
Inhibitor
RAS GTP
C-RAF
B-RAF
MEK
ERK
Growth
P
RAS GTP
C-RAF
B-RAF
Inhibitor
MEK
ERK
Growth
P
RAS GTP
C-RAF
B-RAF
Inhibitor
MEK
ERK

NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE
E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

19 Ottobre 2015

Potenziamento della radiotossicità associata a Zelboraf® (vemurafenib)

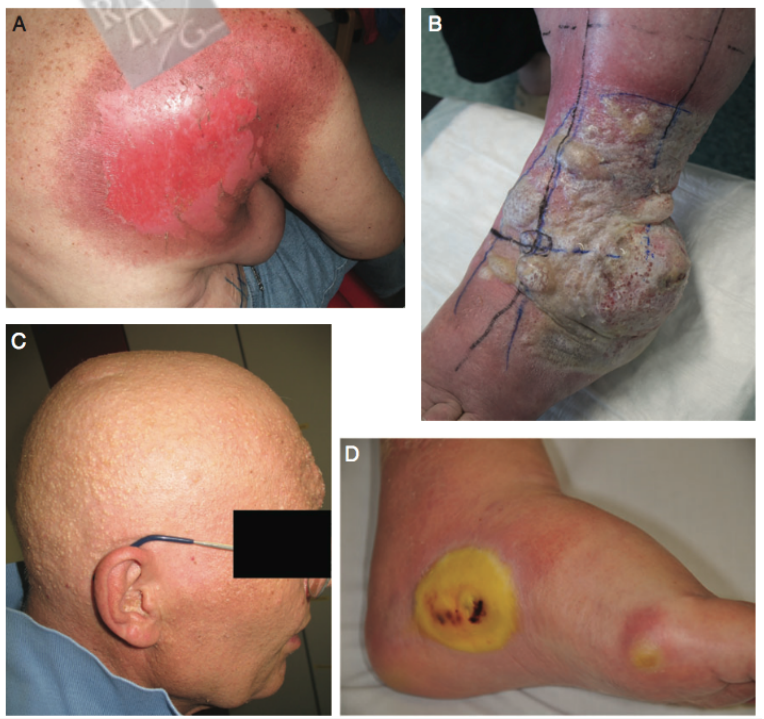
- Casi severi di lesioni correlate a radiazioni, alcuni con esito fatale, sono stati riferiti in pazienti sottoposti a radioterapia prima, durante o dopo il trattamento con Zelboraf.
- La maggior parte dei casi è stata di natura cutanea, ma alcuni casi hanno coinvolto gli organi viscerali.
  - radionecrosis after brain stereotactic radiosurgery.
  - radiation-induced anorectitis complicated by diarrhoea, anorexia and weight loss following the concomitant radiation of a primary rectal tumour
  - radiation recall dermatitis
  - radiation recall pneumonitis
- Zelboraf deve essere usato con cautela quando è somministrato prima, in concomitanza o in sequenza il trattamento radiante.

Radiosensitization by BRAF inhibitor therapy—mechanism and frequency of toxicity in melanoma patients

M. Hecht[1], L. Zimmer[2], C. Loquai[3], C. Weishaupt[4], R. Gutzmer[5], I

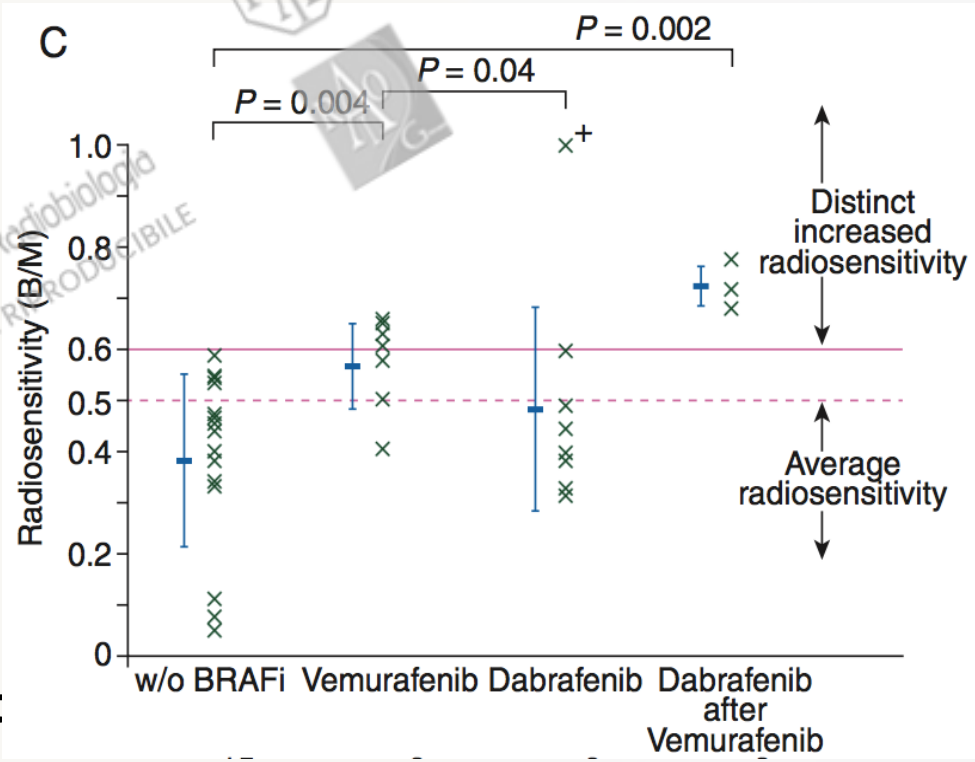
Annals of Oncology 26, 2015

- 161 pts, 70 rt + BRAFi
- **Acute** radiodermatitis ≥°2 of 36%
- No severe **late** skin-related toxicities were reported (mean follow-up 6.6 months).
- Non-skin tox rare.

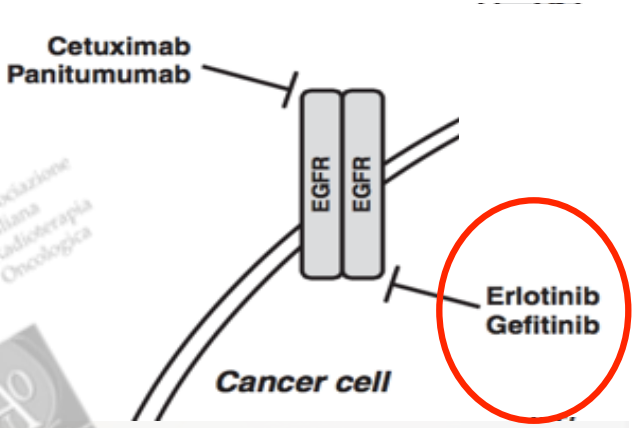


Gestione tox: no RT + anti BRAF?

- Radiodermatitis ≥°2
  - vemurafenib (40%)
  - dabrafenib (26%).
- Possible explanation:
  - Selective affinity of dabrafenib to mutant BRAF
- **Recomandations:**
  - with planned radiotherapy **favor dabrafenib**.
  - **Switching** patients from vemurafenib to dabrafenib before radiotherapy **not recommended.**



Pulmonary toxicities in anti-EGFR TKI Radiation recall?



- Gefitinib (Iressa) Anti-EGFR TKI
  - FDA analysis of 50,000 pts with gefitinib, 1% (ILD)
  - ILD develops within 3–7 weeks after initiating therapy.
  - Approximately 90% of pts who develop gefitinib-induced ILD have received prior radiation or chemotherapy.
  - Mechanism: decrease in alveolar regeneration, (regulated by EGFR)
  - Up to 40% of cases are fatal.

- Erlotinib (Tarceva) anti HER1/EGFR TKI
  - In the FDA approval report for erlotinib the overall incidence of ILD was 8%

Barber NA Targ Oncol (2011) 6:235–243

Radiation recall EGFR-TKI

C.-L. Chiang et al. / Journal of the Chinese Medical Association 79 (2016) 248e255

- 213 pts EGFR-TKI within 5 y after RT.
  - 4.4% RRP (none fatal),
  - ILD 4.4% (mortality rate 71.4% despite aggressive medical treatment),
  - drug-related pneum. 3.9%.
- **Recomandations:**
  - RRP risk is 10-fold higher when the interval between radiotherapy and EGFR-TKI is < 90 days.
  - Hold TKI+steroid = non change,
  - No EGFR-TKI + steroid = improvement in 2 weeks

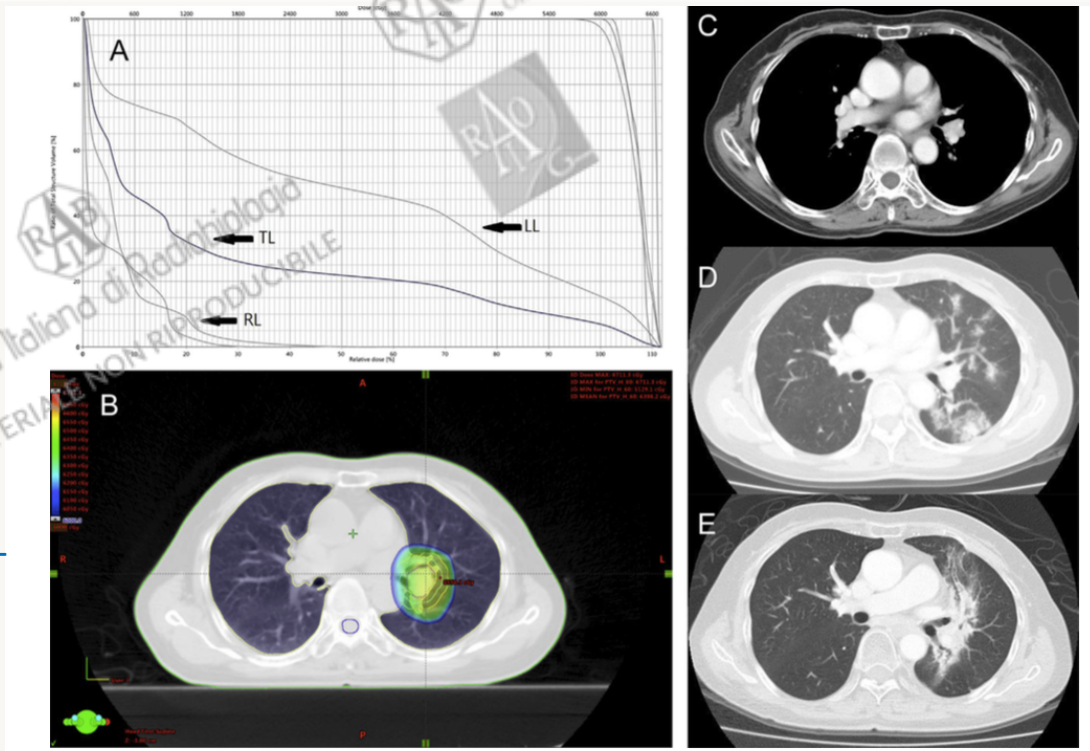


Fig. 2. A representative case with epidermal growth factor receptor-tyrosine kinase inhibitor-related radiation recall pneumonitis (Case 3): (A) the dose-volume histogram of thoracic radiotherapy; (B) computed tomography (CT)-based three dimensional-conformal radiotherapy plan; (C) CT scan of chest obtained before radiotherapy; (D) CT scan after the end of radiotherapy; and (E) radiation pneumonitis induced by erlotinib, which developed 126 days after the end of radiotherapy. LL = left lung; RL = right lung; TL = total lung.

Associazioni RT e nuovi farmaci

The main scenarios are

- 1) RT as the main treatment associated with new drugs
- 2) RT given to metastatic patients treated with innovative drugs
- **3) RT used with immune therapies**

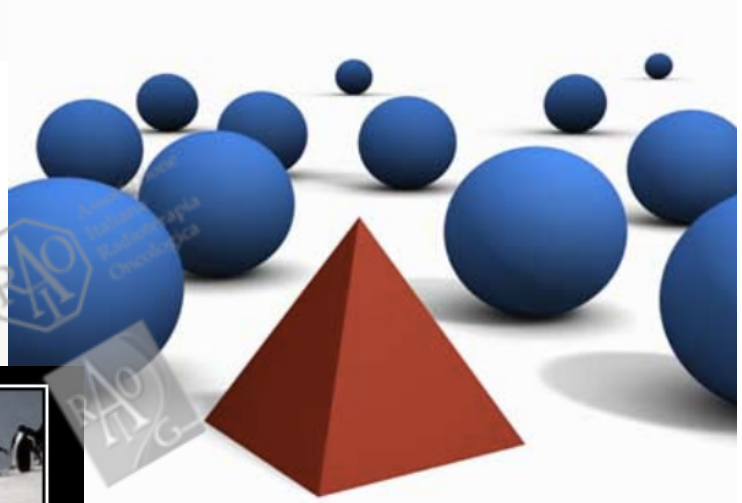
Table 3. Adverse Events.*

Event	Nivolumab (N=313)		Nivolumab plus Ipilimumab (N=313)		Ipilimumab (N=311)	
	Any	Grade 3 or 4	Any	Grade 3 or 4	Any	Grade 3 or 4
	number of patients with event (percent)					
Any adverse event	311 (99.4)	136 (43.5)	312 (99.7)	215 (68.7)	308 (99.0)	173 (55.6)
Treatment-related adverse event†	257 (82.1)	51 (16.3)	299 (95.5)	172 (55.0)	268 (86.2)	85 (27.3)
Diarrhea	60 (19.2)	7 (2.2)	138 (44.1)	29 (9.3)	103 (33.1)	19 (6.1)
Fatigue	107 (34.2)	4 (1.3)	110 (35.1)	13 (4.2)	87 (28.0)	3 (1.0)
Pruritus	59 (18.8)	0	104 (33.2)	6 (1.9)	110 (35.4)	1 (0.3)
Rash	81 (25.9)	2 (0.6)	126 (40.3)	15 (4.8)	102 (32.8)	6 (1.9)
Nausea	41 (13.1)	0	81 (25.9)	7 (2.2)	50 (16.1)	2 (0.6)
Pyrexia	18 (5.8)	0	58 (18.5)	2 (0.6)	21 (6.8)	1 (0.3)
Decreased appetite	34 (10.9)	0	56 (17.9)	4 (1.3)	39 (12.5)	1 (0.3)
Increase in alanine aminotransferase level	12 (3.8)	4 (1.3)	55 (17.6)	26 (8.3)	12 (3.9)	5 (1.6)
Vomiting	20 (6.4)	1 (0.3)	48 (15.3)	8 (2.6)	23 (7.4)	1 (0.3)
Increase in aspartate aminotransferase level	12 (3.8)	3 (1.0)	48 (15.3)	19 (6.1)	11 (3.5)	2 (0.6)
Hypothyroidism	27 (8.6)	0	47 (15.0)	1 (0.3)	13 (4.2)	0
Colitis	4 (1.3)	2 (0.6)	37 (11.8)	24 (7.7)	36 (11.6)	27 (8.7)
Arthralgia	24 (7.7)	0	33 (10.5)	1 (0.3)	19 (6.1)	0
Headache	23 (7.3)	0	32 (10.2)	1 (0.3)	24 (7.7)	1 (0.3)
Dyspnea	14 (4.5)	1 (0.3)	32 (10.2)	2 (0.6)	13 (4.2)	0
Treatment-related adverse event leading to discontinuation	24 (7.7)	16 (5.1)	114 (36.4)	92 (29.4)	46 (14.8)	41 (13.2)

Ipilimumab + RT melanoma brain metastases

Study (author, year)	N					Radiation necrosis requiring surgery
Kiess 2015	46	54% 3 mg/kg 4 cycles, 46% 10 mg/ kg 4 cycles. 28% received maintenance	SRS 21 Gy (15-24), 20% WBRT after recurrence	typical systemic immune-related (enterocolitis, pruritus, and hepatitis).	Hemorragies common after SRS during Ipi (40%.) • **6% G3** CNS bleeding SRS **before/after Ipi** • **13% G3** CNS bleeding SRS **during Ipi**,	5 pts
Gerber 2015	13	70% 4 cycles ipilimumab 3 mg mq q 21, 30% 2 cycles	WBRT	nd	77% new hemorragic foci	nd
Patel 2015	34 SRS, 20 SRS+ Ipi	Ipi 3mg/kg within 4 months. No maintenance	SRS 21-15 Gy	nd	At 1 year, with ipilimumab and SRS trend toward **higher rates of radiation necrosis** (30.0% vs. 20.92%, *P* = 0.078)	No difference (15.0% vs. 14.7%, *P* = 1.00)

Dati!



- Frazionamenti

- Associazione temporale

- Tox sede specifiche e tumore-specifiche

3/27

"I know nothing about the subject,
but I'm happy to give you my expert opinion."