SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

UNIVERSITÀ DEGLI STUDI DI FERRARA
- EX LABORE FRUCTUS -

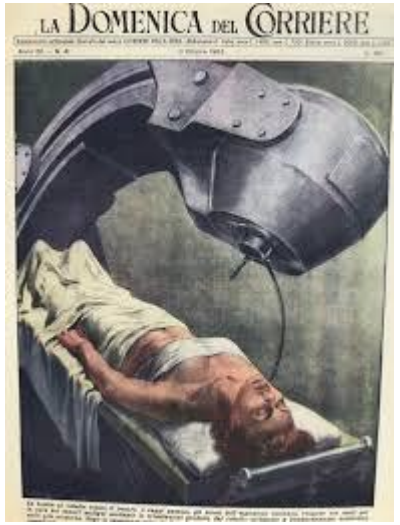
Azienda Unità Sanitaria Locale
Ferrara

Società Medico Chirurgica di Ferrara

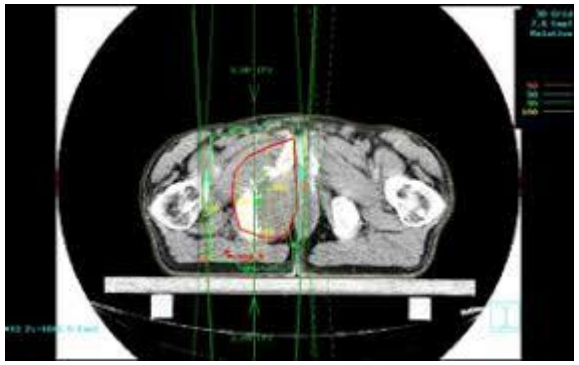
Melanoma : altri approcci terapeutici Radioterapia ed elettrochemioterapia

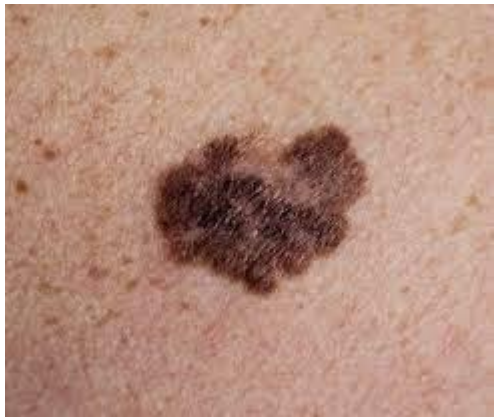
Ferrara 23.11.2024

Ospedale S. Anna
Dipartimento Oncoematologico
Unità Operativa di Radioterapia
Direttore Dott. A. Stefanelli



Historically, melanoma cells were considered to be radioresistant, hence the role of RT was mainly limited to the symptomatic treatment of advanced disease.





ACTA RADIOLOGICA

Vol. 25 Fasc. 1 | ONCOLOGY | 1986 January–February

REVIEW ARTICLE

RADIATION BIOLOGY OF MALIGNANT MELANOMA

radioresistente

E. K. ROFSTAD

Abstract

The survival curves for melanoma cells exposed to single radiation doses in vitro and the specific growth delays for melanoma xenografts irradiated with single doses in vivo were found to differ considerably among individual cell lines and tumours. In fact, the differences could be almost as large as the largest differences observed among cell lines and xenografts from tumours of different histology with very different clinical radiocurability. Moreover, radiobiologic parameters that may have significant influence on tumour response to fractionated irradiation, e.g. growth rate, hypoxic fraction, reoxygenation ability, PLD-repair capacity and contact repair capacity, were found to differ greatly in magnitude among individual melanomas. This review therefore concludes that malignant melanoma is a tumour type that is very heterogeneous in radioresponsiveness, i.e. malignant melanomas should no longer be considered to be radiation resistant in general. The values of the α/β ratio derived from cell

the suggestion that the radiation therapy of this disease might be improved by use of fractionation regimes with fewer fractions and higher doses per fraction than used in conventional regimes (30 fractions of 2.0 Gy over 6 weeks) (13). The subsequent discussion in the literature supported this suggestion in general, although there was some disagreement on the absolute magnitude of the superiority of high fraction radiation regimes (81, 82, 85, 86). Moreover, the first clinical investigations indicated that melanomas showed better response when treated with 4 to 8 Gy fractions than with 2 to 3 Gy fractions (29, 33).

Since then, the radiation biology of malignant melanoma has received much attention. Studies in vitro have been carried out using several established human cell lines

Treating Melanoma Skin Cancer

If you've been diagnosed with melanoma, your treatment team will discuss your treatment options with you. It's important to weigh the benefits of each treatment option against the possible risks and side effects.

How is melanoma skin cancer treated?

Based on the stage of the cancer and other factors, your treatment options might include:

- Surgery for Melanoma Skin Cancer
- Immunotherapy for Melanoma Skin Cancer
- Targeted Therapy Drugs for Melanoma Skin Cancer
- Chemotherapy for Melanoma Skin Cancer
- Radiation Therapy for Melanoma Skin Cancer

Common treatment approaches

Early-stage melanomas can often be treated with surgery alone, but more advanced cancers often require other treatments. Sometimes more than one type of treatment is used.

Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 4, pp. 1051–1055, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.05.056

CLINICAL INVESTIGATION **Skin**

ADJUVANT RADIOTHERAPY FOR CUTANEOUS MELANOMA: COMPARING HYPOFRACTIONATION TO CONVENTIONAL FRACTIONATION

DANIEL T. CHANG, M.D., ROBERT J. AMDUR, M.D., CHRISTOPHER G. MORRIS, M.S., AND WILLIAM M. MENDENHALL, M.D.

Department of Radiation Oncology, College of Medicine, University of Florida, Gainesville, FL

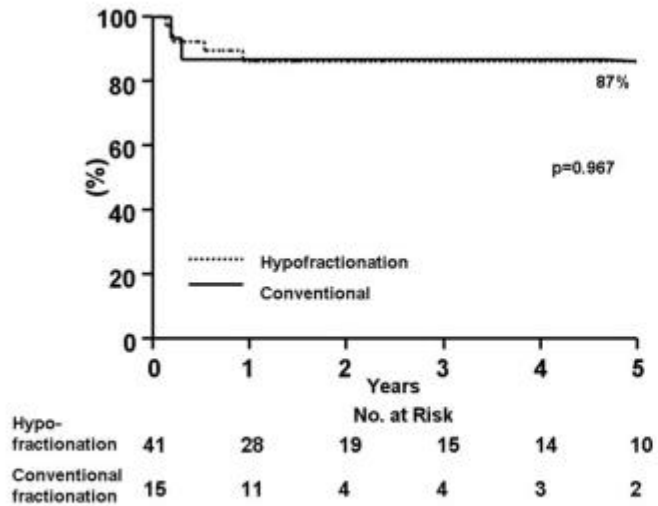


Fig. 2. In-field locoregional control rates according to fractionation schedule.

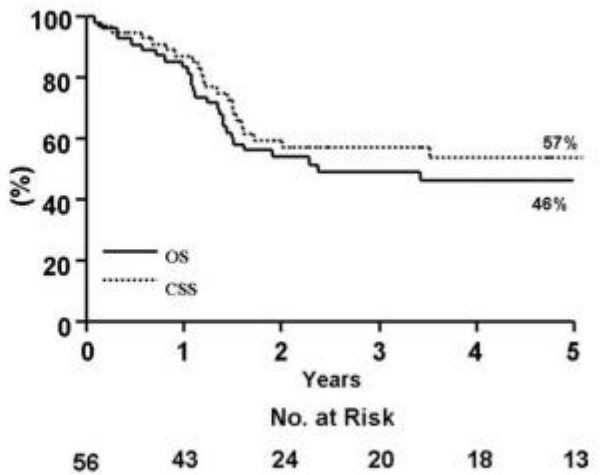


Fig. 3. Overall survival (OS) and cause-specific survival (CSS) after treatment.

VIA MEDICA

REVIEW ARTICLE

Mateusz Spałek, Anna M Czarnecka

Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Skłodowska-Curie Institute — Oncology Centre, Warsaw, Poland

The role of radiotherapy in melanoma

role in the treatment of melanoma is constantly evolving

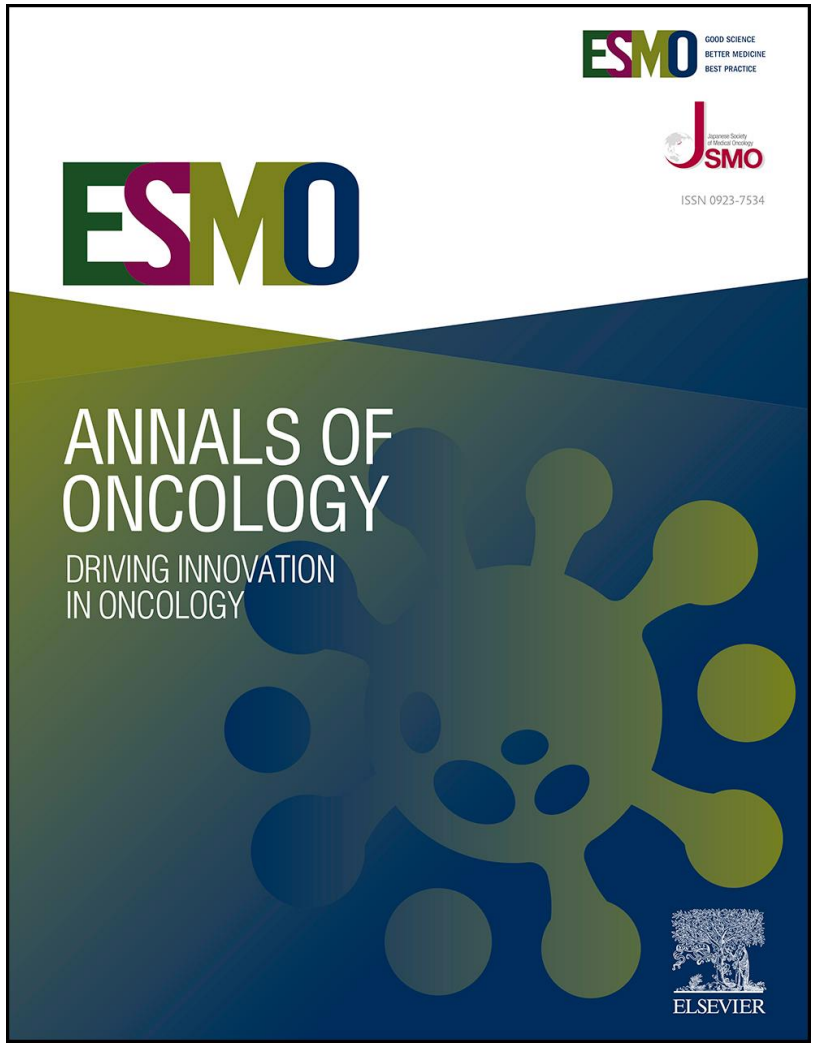
Table 1. Evolution of the role of radiotherapy in melanoma treatment

Radiotherapy type	Past	Present
Adjuvant after lymphadenectomy	+++	+
Palliative	+++	++*
Whole brain radiotherapy	+++	+
Adjuvant after primary tumour resection	++	+
Definitive	+	++*
Oligometastatic disease	+	++*#
Oligoprogression	–	+++*#
"Boost" during immunotherapy	–	+++?*

*Including stereotactic techniques

#Also treatment of brain metastases with radiosurgery

Oncology in Clinical Practice
2019, Vol. 15, No. 6, 310–319



Adjuvant RT

- Adjuvant RT is not routinely recommended [III, D].

- RT can be considered for local tumour control in cases of inadequate resection margins of lentigo maligna [III, B].

- Adjuvant RT to the primary excision site should be considered for patients with desmoplastic or neurotropic melanoma for whom adequate (≥8 mm) pathological resection margins cannot be achieved [IV, C].

- RT could be discussed for patients with an R1 resection (resection with microscopic tumour at the margin) or after resection of bulky LN metastases, especially if further surgical clearance is not feasible [III, C]

RT is rarely used to treat non-metastatic melanoma while it plays an important role in metastatic disease RT should be used in as much as 23% of patients with advanced melanoma

About 15% of patients with melanoma have metastatic disease at diagnosis or will develop metastatic disease during their illness

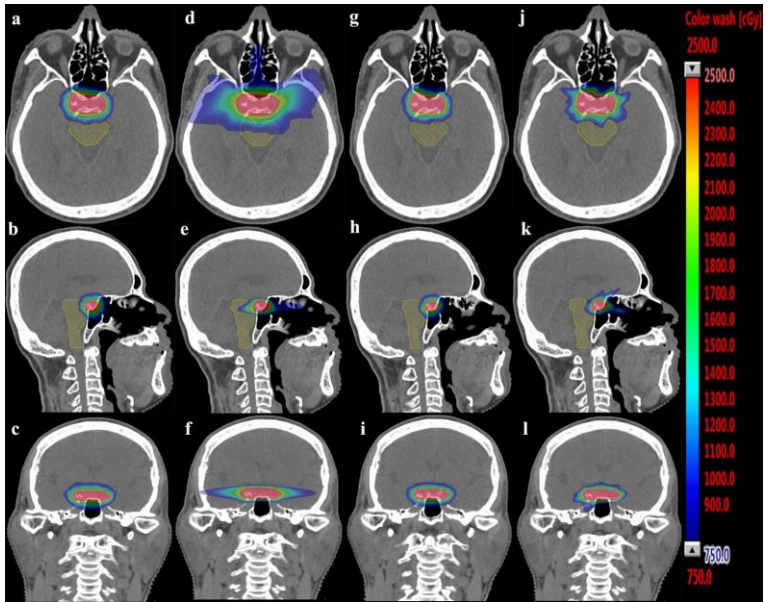
National Comprehensive Cancer Network
Cancer Med. 2015;4(1):1–6.

RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA

Razionale Clinico

- Erogare una dose elevata di radiazioni ionizzanti all'interno di un volume bersaglio di dimensioni limitate

- Contenere il rilascio di dosi clinicamente significative ai tessuti sani circostanti sfruttando la rapida caduta di dose (gradiente di dose) al di fuori del volume definito



FRAZIONAMENTI

ENCEFALO (Metastasi cerebrali)

RADIOCHIRURGIA

- 24 Gy/1ff

RADIOTERAPIA STEREOTASSICA

- 27-30 Gy/3ff
- 30Gy/5ff

EXTRACRANICA

RADIOCHIRURGIA

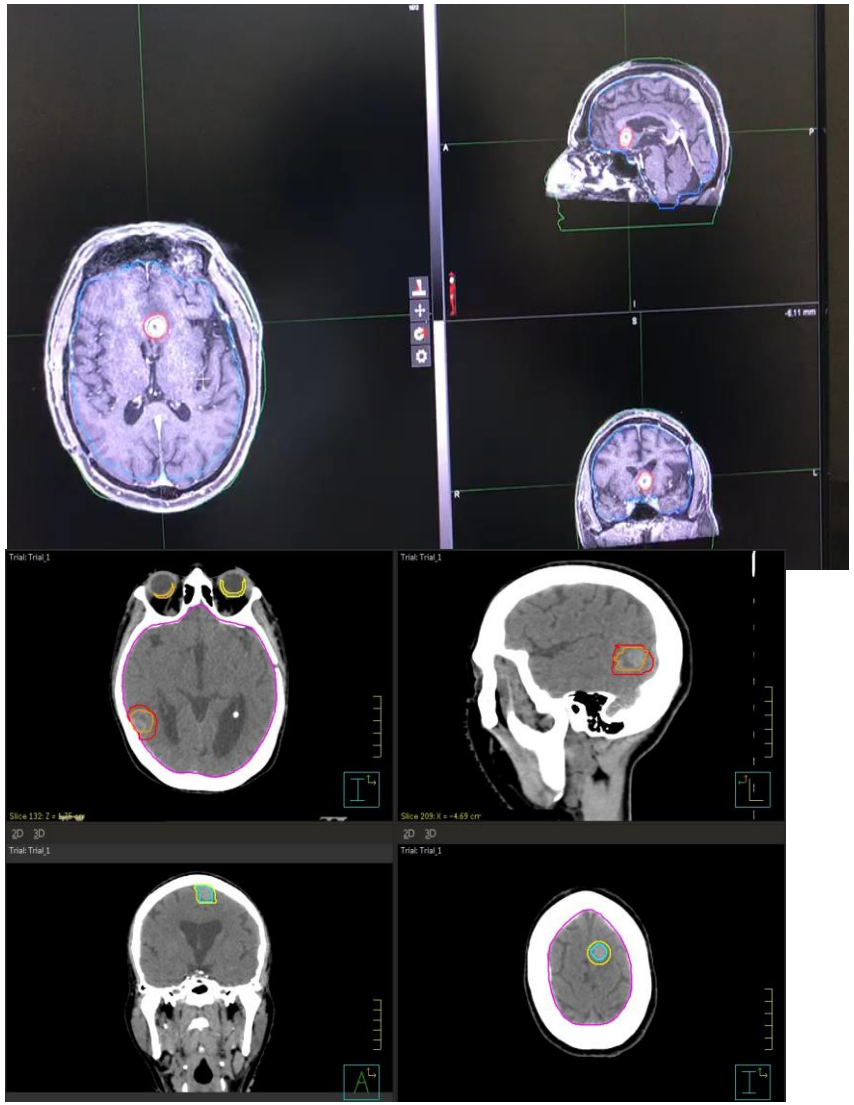
- 24-30 Gy/1ff

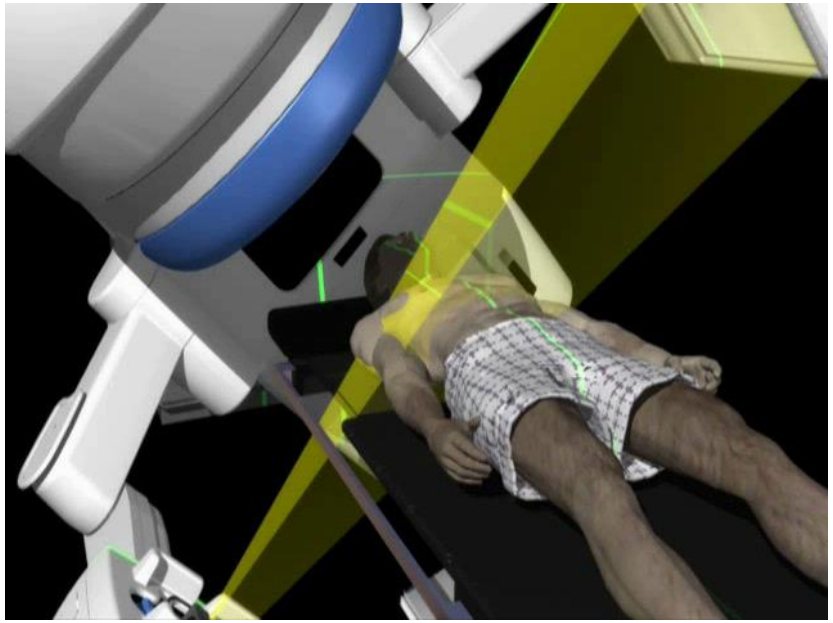
RADIOTERAPIA STEREOTASSICA

- 45Gy/3ff
- 48 Gy/4ff
- 50Gy/5ff

STEREOTASSI ENCEFALICA

Imaging Multimodale (TAC/RM)





RT in combination with molecularly targeted therapy

- BRAF inhibitors with simultaneous RT are contradictory, and the use of such a combination requires caution.
- Some reports suggest an advantage of using the combination in sensitising melanoma cells to RT after the administration of BRAF inhibitors

frontiers in Oncology

CASE REPORT
published: 26 March 2019
doi: 10.3389/fonc.2019.00168

Targeted Therapy After Brain Radiotherapy for BRAF-Mutated Melanoma With Extensive Ependymal Disease With Prolonged Survival: Case Report and Review of the Literature

OPEN ACCESS Ibrahim Abu-Gheida[1†], Samuel Chao[1], Erin Murphy[1], John Suh[1], Glen H. Stevens[2],

RT in combination with immunotherapy

- This is confirmed by increased frequency of an extremely rare phenomenon known as the **abscopal effect** (response of untreated
- lesions as consequence of local treatment of another lesion) with simultaneous use of RT with immunotherapy

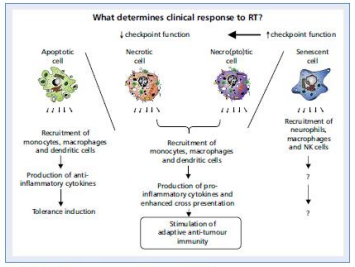


Figure 3. Immunological factors determing response to radiotherapy [43]

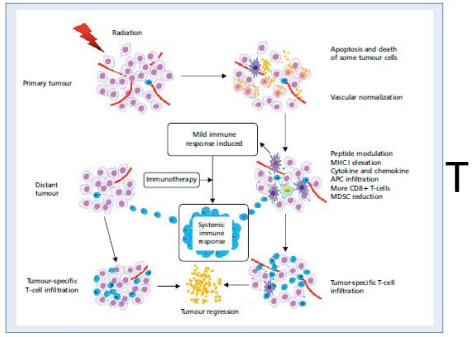


Figure 4. Mechanism of radiotherapy and immunotherapy synergy [44]

T cell CD8+

Research Article

Cancer Immunology Research

PD-1 Restrains Radiotherapy-Induced Abscopal Effect

Sean S. Park[1], Haidong Dong[2,3], Xin Liu[3], Susan M. Harrington[3], Christopher J. Krco[3], Michael P. Grams[1], Aaron S. Mansfield[4], Keith M. Furutani[1], Kenneth R. Olivier[1], and Eugene D. Kwon[2,3]

Abstract

The NEW ENGLAND JOURNAL of MEDICINE

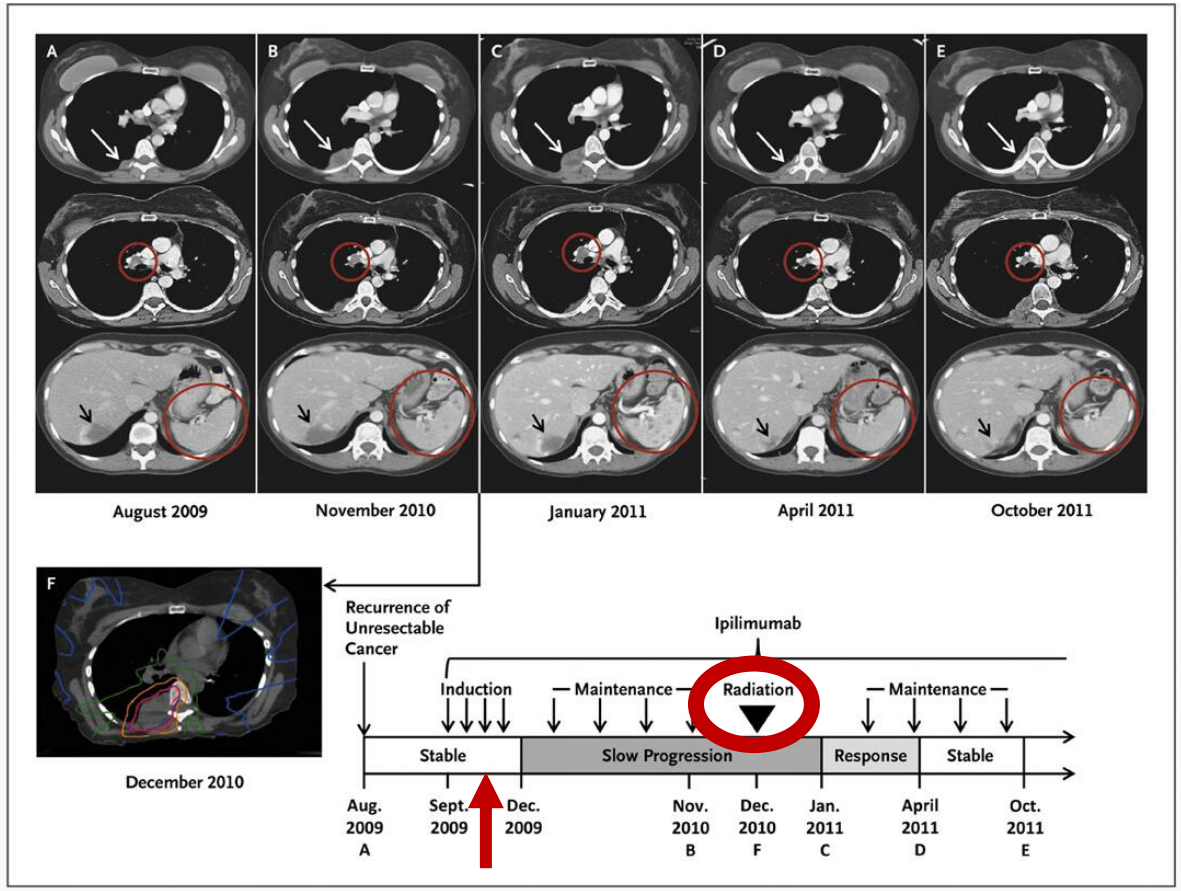
ORIGINAL ARTICLE | BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Authors: Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., +13, and Jedd D. Wolchok, M.D., Ph.D. Author Info & Affiliations

Published March 8, 2012 | N Engl J Med 2012;366:925-931 | DOI: 10.1056/NEJMoa1112824 | VOL. 366 NO. 10

Abstract



RT

Cancer Medicine

Open Access

ORIGINAL RESEARCH

Ipilimumab and radiation therapy for melanoma brain metastases

Ann W. Silk[1], Michael F. Bassetti[2], Brady T. West[3], Christina I. Tsien[4] & Christopher D. Lao[1]

[1]Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan
[2]Department of Human Oncology, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin
[3]Institute for Social Research, University of Michigan, Ann Arbor, Michigan
[4]Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan

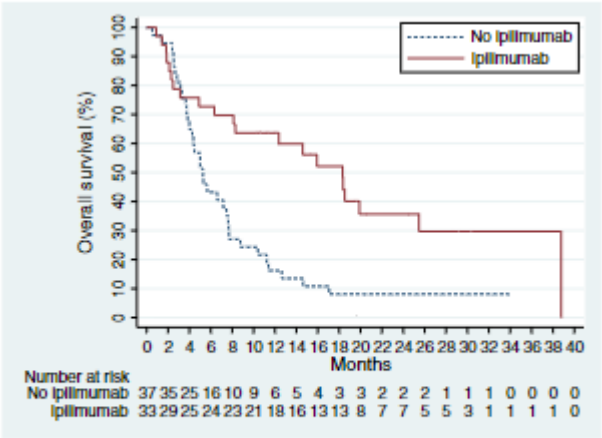
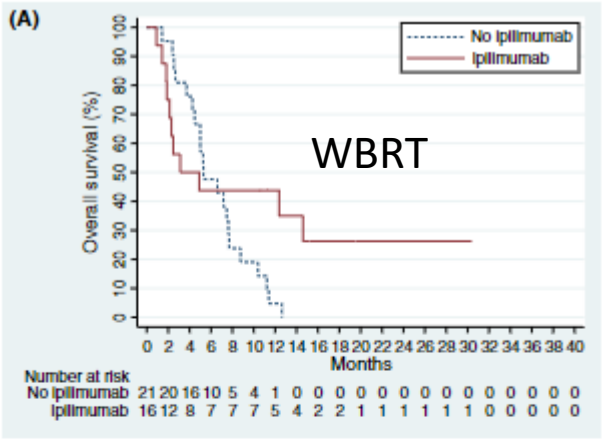


Figure 1. Censored overall survival of all patients by ipilimumab treatment. Treatment with ipilimumab was significantly associated with improved survival (HR – 0.43, *P* – 0.005). HR, hazard ratio.



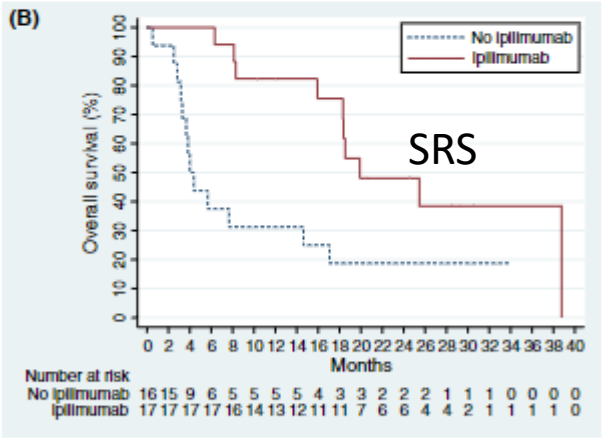
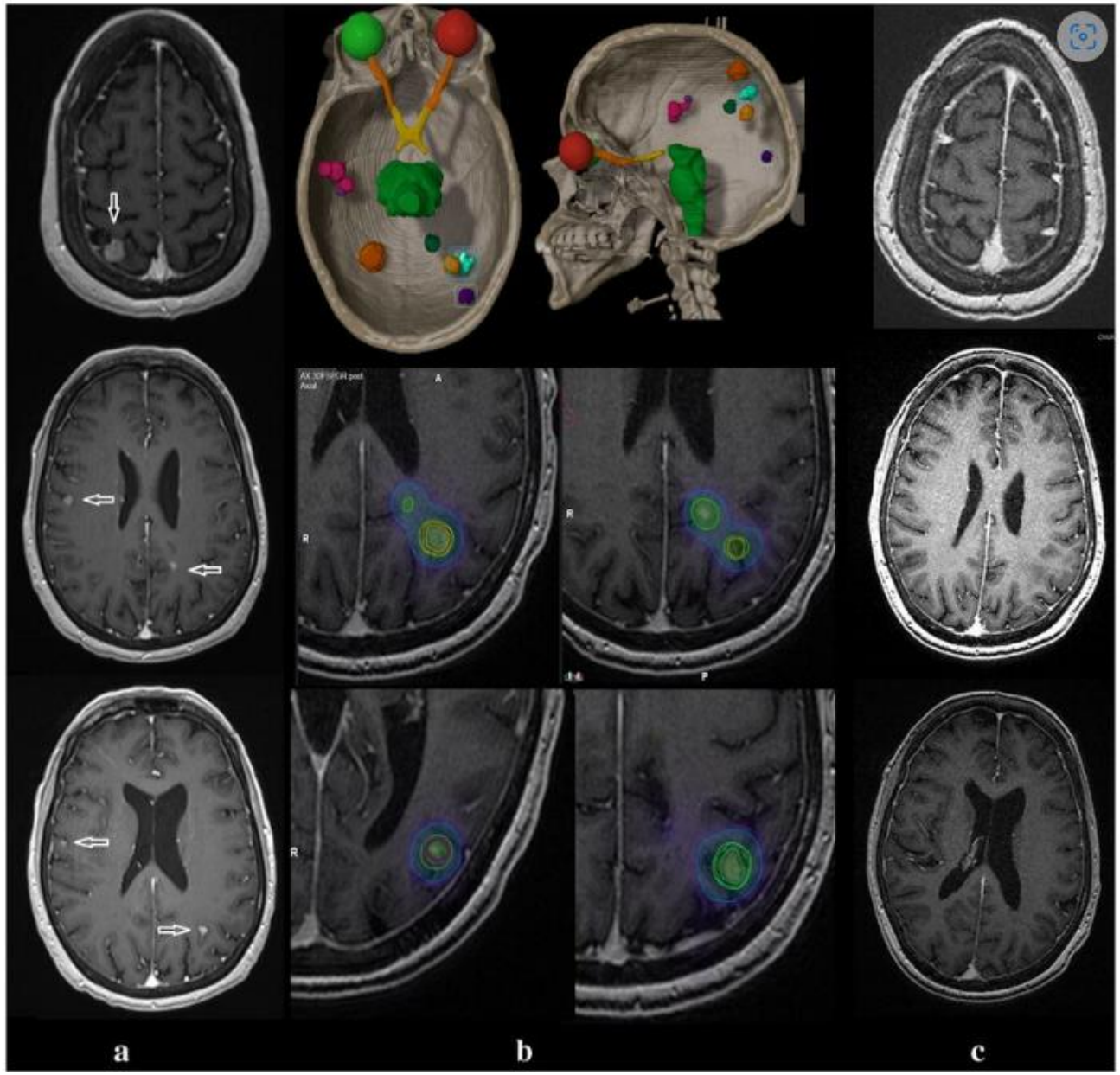


Figure 2. Censored overall survival of patients for each type of radiation therapy by ipilimumab treatment. (A) WBRT: treatment with ipilimumab was not associated with survival in the subset of patients who underwent WBRT (HR – 0.56, *P* – 0.15); (B) SRS: treatment with ipilimumab was significantly associated with improved survival in the subset of patients who underwent SRS (HR – 0.31, *P* – 0.009). WBRT, whole brain radiation therapy; HR, hazard ratio; SRS, stereotactic radiosurgery.



Patient with 8 melanoma brain metastases was treated with stereotactic radiosurgery (SRS). a Baseline MRI showing metastatic lesions. b SRS planning with bird's-eye view and planning isodose lines. c Follow-up MRI after 5 months showing near complete resolution of all lesions. However, this patient developed new cerebellar lesion 8 months after initial SRS which was also treated with SRS

Conclusions

RT has an important role in the treatment of patients with melanoma;

however, the indications for RT in melanoma have changed significantly over the past few years.

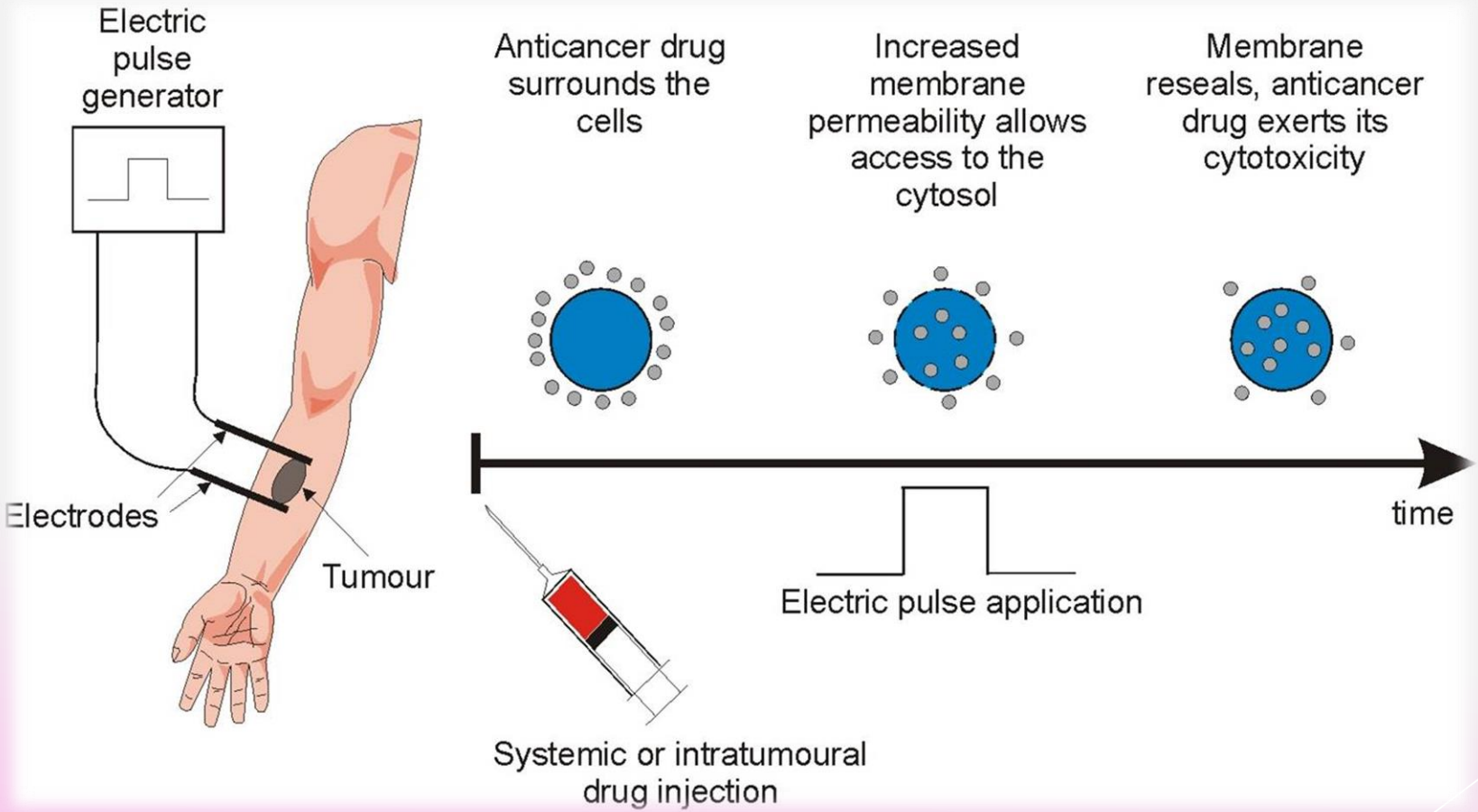
Indications for palliative RT remain unchanged.

Adjuvant RT after lymphadenectomy is not recommended because more effective adjuvant treatments are available.

RT is increasingly used to enhance the effectiveness of immunotherapy and targeted therapy, as well as to delay the withdrawal of effective systemic therapy in the case of oligoprogression.

This topic requires new prospective clinical trials; however, emerging data justify the use of RT in the described clinical situations. Since the response to RT is partly dependent on CD8+ T-cells, developing future strategies to increase T-cell infiltration may improve the effectiveness of RT in melanoma patients.

ELECTROCHEMOTHERAPY

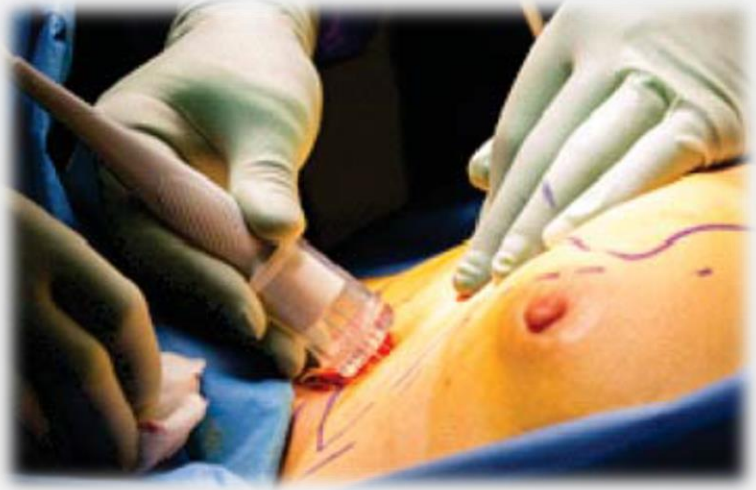


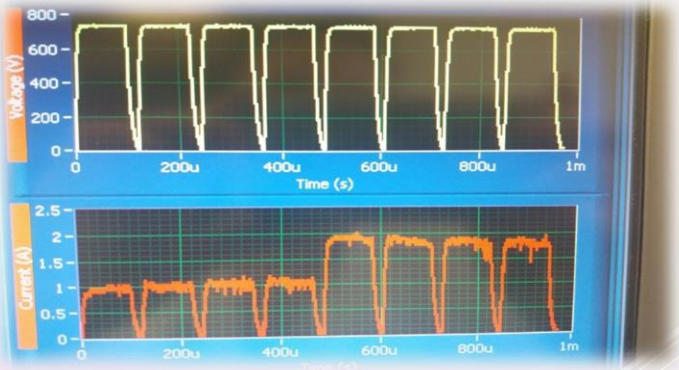
ELECTROCHEMOTHERAPY

Linear

Hexagonal

Plate





LITERATURE ON ECT IN MELANOMA SKIN METASTASES

- Actuarial **LC** was reported in four studies: 72-87% 2-year LC
- Three papers analyzed **OS**: 67-86.2% 1-year OS
- Campana et al. reported 87% 2-year local **PFS**
- **Melanoma specific survival** was reported by Kunte et al. as 74% 1-year rate

TOXICITY

Author/year	Toxicity
Rudolf Z. et al, 1995	erythema, muscle spasm, local pain
Glass LF. et al, 1996	erythema and edema
Rols MP. et al, 2000	erythema, edema, superficial necrosis, hyperthermia,
Sersa G. et al, 2000	erythema
Sersa G. et al, 2000	erythema and edema
	pain, muscle spasm
	pain 75%, muscle spasm 25%, erythema 16.6%, necrosis 41.6%
	erythema 21.4%, pain 0%
	erythema, edema
Campana LG. et al, 2012	pain 92%, syncope 4.7%, nausea 9.4%, fever 4.7%, skin G3 18%
Ricotti F. et al, 2014	NR
Mir-Bonafè JM. et al, 2015	ulceration and infection (25.8%), pain, edema, erythema, nausea, vomiting
Caracò C. et al, 2015	pain 37%, myalgia 13.5%, necrosis 29.2%
Mozzillo N. et al, 2015	pruritus 80%
Hribernik A. et al, 2016	None
Heppt M. et al, 2016	ulceration 45.5%, erythema 42.4%, infection 30.3%, pain 24.2%, nausea 9.%% ≥ G3)
Tomassini GM. et al, 2016	NR
Kunte C. et al, 2017	skin toxicity 50% (G3 in 2 pts), nausea 4%, lymphedema 4%, flu like symptoms 5%, pain 39%

Pain:24.2-92.0%
Erythema:16.6-42.0%
Necrosis: 29.2-41.6%

ECT AND IMMUNOTHERAPY

Cancers (Basel). 2021 Sep; 13(17): 4289.
Published online 2021 Aug 25. doi: 10.3390/cancers13174289
PMCID: PMC8428335
PMID: 34503099

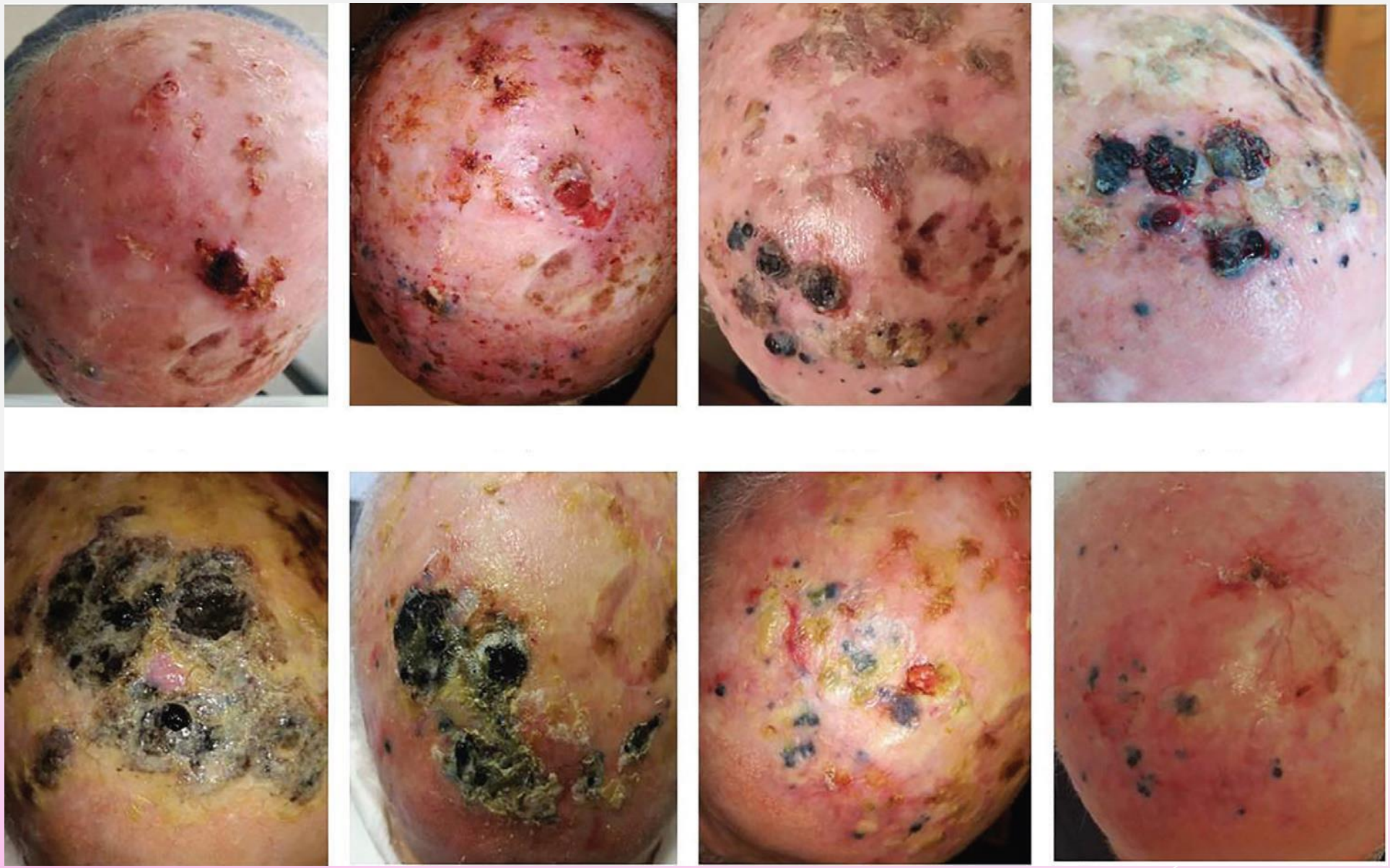
Combination of Pembrolizumab with Electrochemotherapy in Cutaneous Metastases from Melanoma: A Comparative Retrospective Study from the InspECT and Slovenian Cancer Registry

Luca G. Campana,[1,*†] Barbara Peric,[2,3,†] Matteo Mascherini,[4] Romina Spina,[5] Christian Kunte,[6,7] Erika Kis,[8]

- stage IIIC–IV melanoma patients
- pembrolizumab alone *vs* pembrolizumab plus ECT *vs* ECT

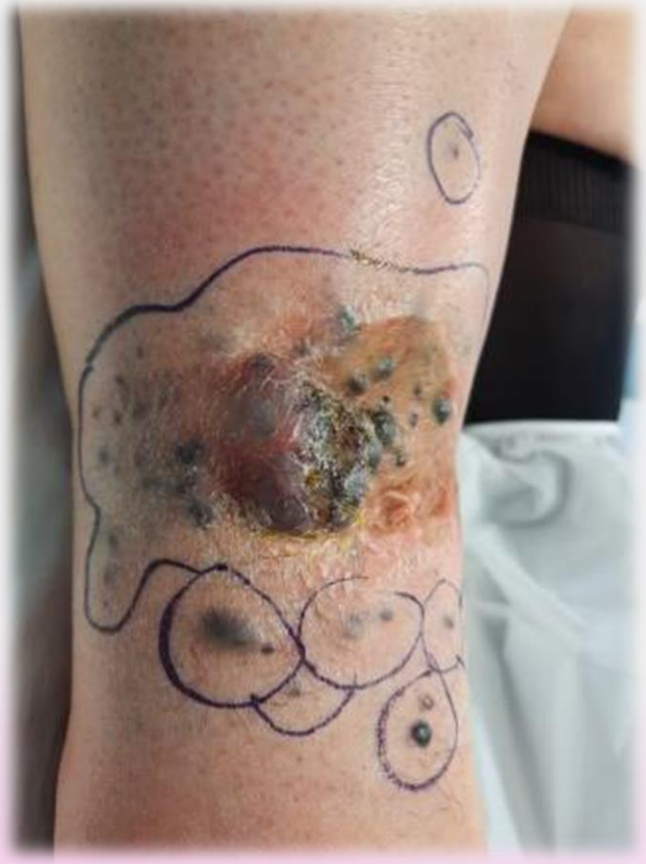
	Pembro+ECT	Pembro	
ORR	78%	39%	P < 0,001
LPFS	86%	51%	P < 0,001
OS	88%	64%	P = 0,006

Campana LG et al., 2021



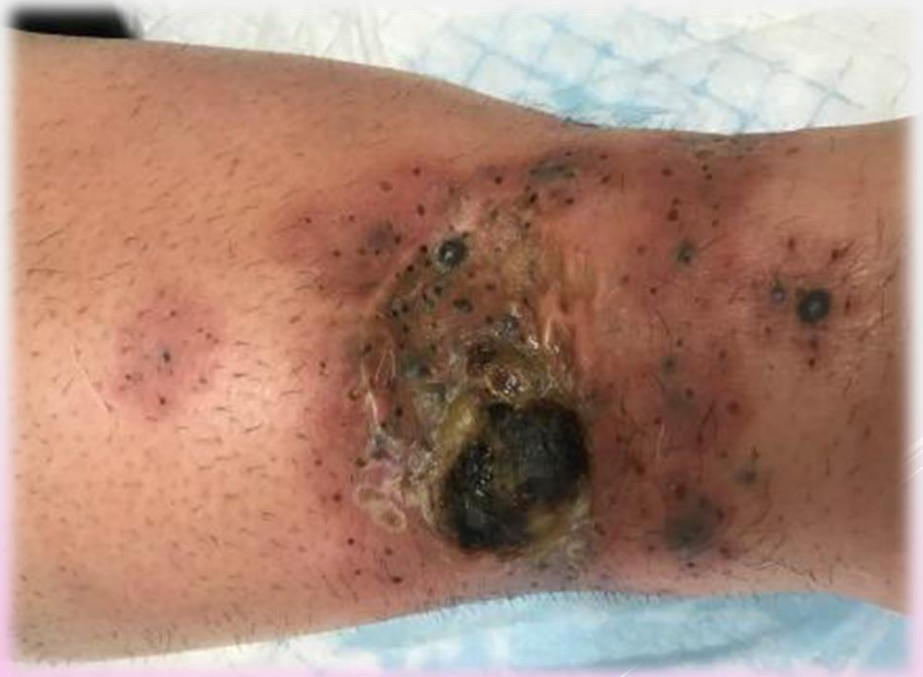
Quaresmini et al., 2021

CLINICAL CASE (2)

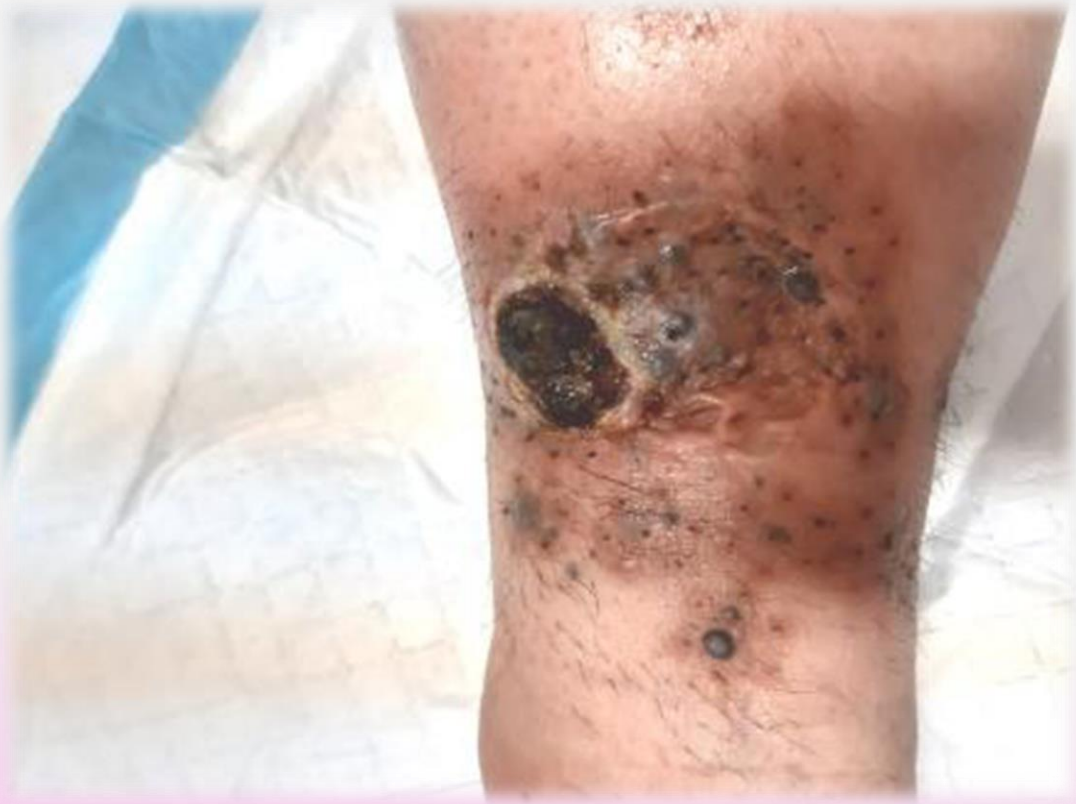


Pre ECT

1 settimana post ECT



CLINICAL CASE (2)



3 settimane post ECT

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

Università degli Studi di Ferrara

Elettrochemioterapia: la nostra esperienza

Dal 2017 al 2024 totale casi: 40

- Melanoma, Ca. Basocellulare, Ca. Spinocellulare: 12
- Recidiva cutanea di carcinoma della mammella: 11
- Ca. Vulva: 6
- Ca. Ano/Retto: 6
- Metastasi Ossee: 4
- Ca. testa/collo: 2
- Neoplasia vie biliari: 1

UOC Chirurgia Senologica
Direttore: Prof. Paolo Carcoforo
Dr.ssa Simona Bonazza

UO Radioterapia Oncologica
Direttore: Dott. Antonio Stefanelli

CONCLUSIONS

- ECT may be considered **a treatment option** in patients with melanoma skin metastases.
- Low grade of available evidence and the need to individualize treatment --- the importance of **multidisciplinary team** including dermatologists, medical oncologists, and radiation oncologists.
- Importance of **patient selection, treatments combinations** (immunotherapy) and **early** ECT treatment