CORSO DI IMMUNOTERAPIA IN ONCOLOGIA
"CARCINOMA DEL RENE E DELLA VESCICA"

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Radioterapia e Immunoterapia: l'oggi e il domani

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Immunotherapy and Tumor

Immune System

The main role of the immune system is to restore normal tissues' homeostasis when altered by pathologic processes, including neoplastic transformation [1]. The immune system is often successful in eliminating neoplastic cells. Thus, all established tumours need to overcome immunity to progress and grow, and most of them successfully escape immune control, through different mechanisms [2,3]. Until recently, attempts in developing and

Melanoma is actually the first cancer subtype where these immune-activating agents showed an advantage in survival over standard chemotherapy, and data from large clinical trials confirmed a substantial benefit with prolonged survival [5].

Filippi AR et al. Radiotherapy and immune checkpoints inhibitors for advanced melanoma. Radiother Oncol (2016),

Immunotherapy & RT

Rationale

radiation is able to convert the tumour in an "in situ" vaccine, altering the microenvironment towards the development of an "immunogenic hub": radiation is in fact able to promote both the priming and effector phases of anti-tumour immune response

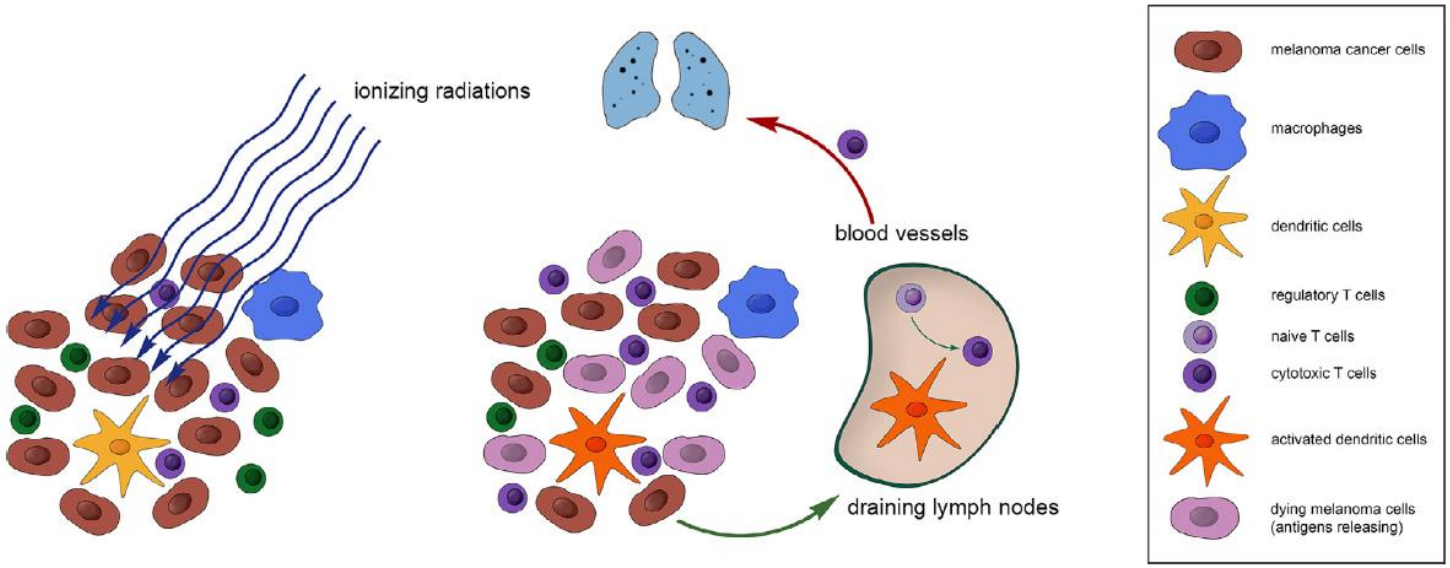

Fig. 1. The "in situ vaccination" concept: ionizing radiation may increase antigens release from dying cancer cells, activate dendritic cells, expand specific anti-melanoma cytotoxic T cells (CTCs) through cross-priming in draining lymph nodes and increase immune response at both local and distant sites [modified from Ref. 52].

Filippi AR et al. Radiotherapy and immune checkpoints inhibitors for advanced melanoma. Radiother Oncol (2016),

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Immunotherapy and Radiotherapy

Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy

Lancet Oncology 2015; 16: e498–509

Andrew B Sharabi, Michael Lim, Theodore L DeWeese, Charles G Drake

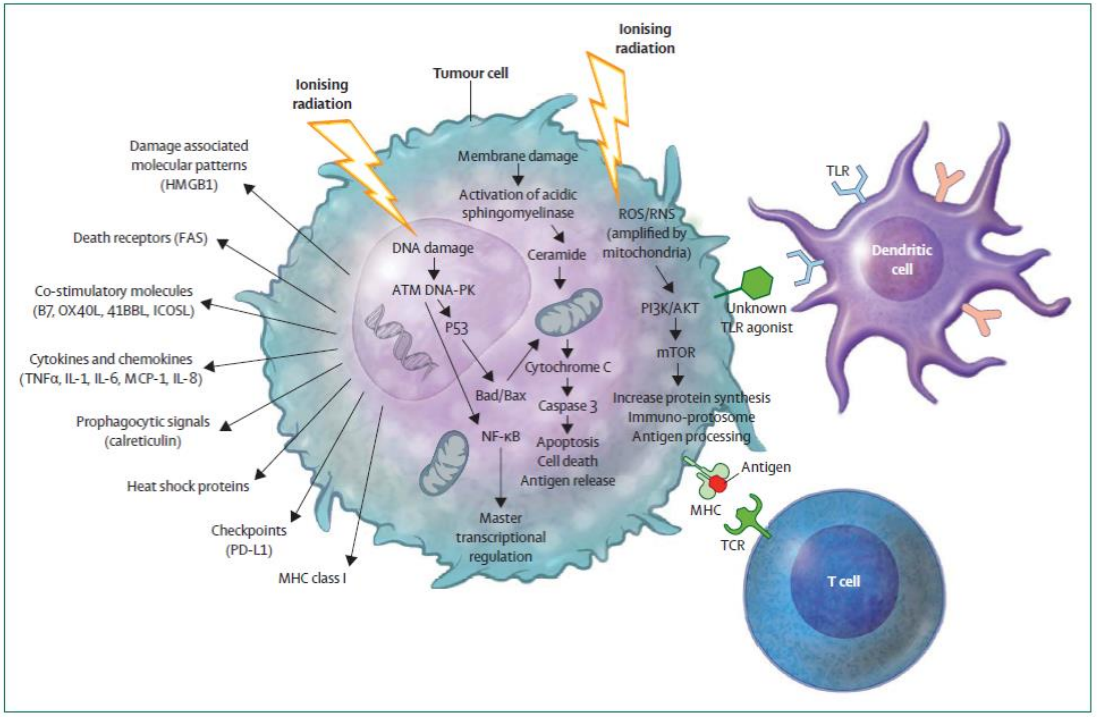

Figure 1: **Radiation induces changes to the tumour cell immunophenotype**
Radiation-induced DNA and membrane damage, and cytoplasmic reactive oxygen species (ROS) activate many transcription factors and signalling pathways that modulate the immunophenotype and immunogenicity of tumour cells. Modified from Finkelstein and colleagues.[34]

Radiation enhances MHC class I surface expression, calreticulin expression, and release of HMGB1

Radiation activates dendritic cells and enhances cross-presentation of tumour antigens

Radiation increases the density of tumour-infiltrating lymphocytes

Radiation modulates the expression of immune checkpoint molecules

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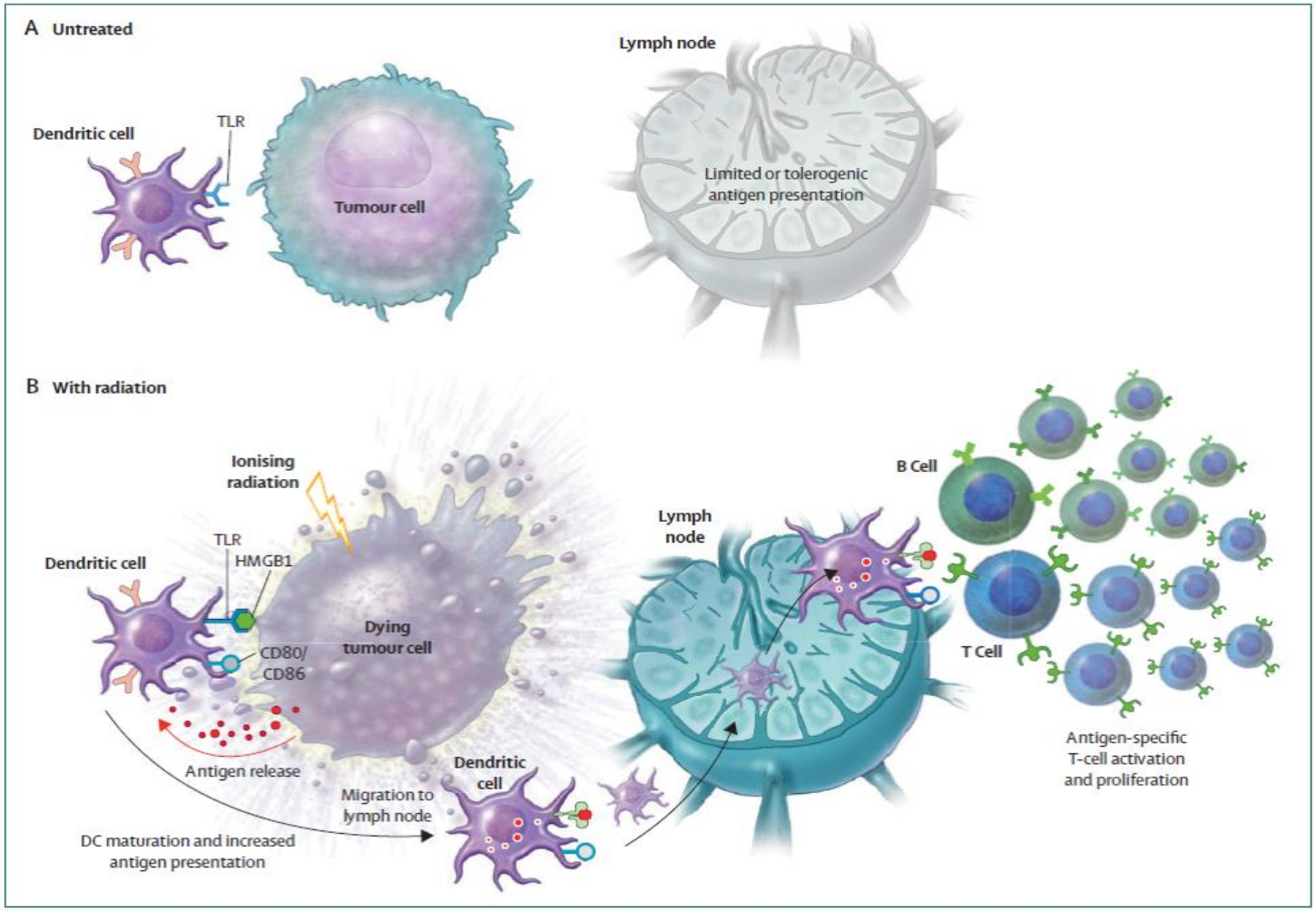


Lancet Oncology 2015; 16: e498–509

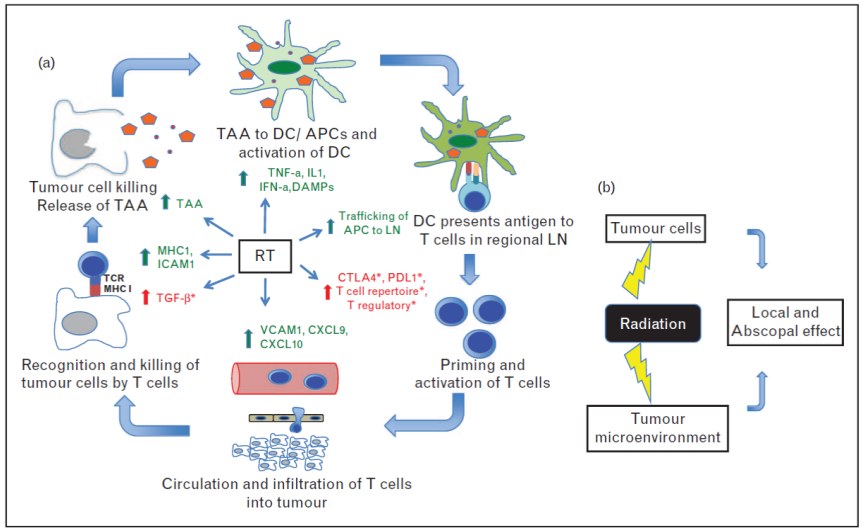
Radiation-induced danger signals enhance dendritic cell-mediated antigen presentation, resulting in activation and proliferation of tumour-specific CD8 T cells.

Immunotherapy and Radiotherapy

Immune checkpoint inhibitors with radiotherapy and locoregional treatment: synergism and potential clinical implications

Curr Opin Oncol 2015, 27:445–451

Angela Esposito, Carmen Criscitiello, and Giuseppe Curigliano



Curr Opin Urol 2016, 26:514–522

EFFECT OF RADIOTHERAPY ON CANCER IMMUNE RESPONSE

Radiotherapy, in addition to a direct cytocidal effect on cancer cells, has also immune modulatory properties; in fact, it causes immunogenic cell death (ICD) of cancer cells, modulates antigen presentation by cancer cells, and most importantly alters the microenvironment within the irradiated field [4,5▪] (Fig. 1). The ICD of cancer cells involves a multistep process, including the release of 'find-me' signals (such as fractalkine, nucleotides, and ATP) that attract phagocytes or dendritic cells, the expression of 'eat-me' signals (such as calreticulin) that facilitate recognition by phagocytes or dendritic cells, and, finally, the release of danger-associated molecular patterns [such as high-mobility group box 1 protein (HMGB1) and ATP] that enable dying tumor cells to lose the propensity to induce tolerance and to stimulate powerful anticancer immune responses [6–8]. Since the resident dendritic cells

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Immunotherapy and RT

- **Cancer Vaccines**
  - Peptides
  - Dendritic Cells
  - Recombinant viruses
- **Antibodies**
  - Anti-CTLA-4
  - Anti-PD-1

Ipilimumab

Nivolumab
Pembrolizumab

Immunotherapy and Radiotherapy and Renal & Bladder cancer

Immunotherapy with radiotherapy in urological malignancies

Curr Opin Urol 2016, 26:514–522

Shaveta Mehta[a,b], *Tim Illidge*[a,b], *and Ananya Choudhury*[a,b]

URINARY BLADDER

The evidence for radiotherapy inducing a cytotoxic immune response in urothelial cancer is long-standing. More than 40 yeas ago, O'Toole *et al.* [41] evaluated the effect of tumour irradiation on peripheral blood lymphocyte (PBL) cytotoxicity in patients with T1–T4 bladder cancer. Two out of three patients with T3 cancer who were negative for PBL cytotoxic activity before radiation were positive afterwards. In a follow-up study [42], the authors demonstrated that patients who were clinically tumour-free for 5 years after treatment had a more rapid postradiotherapy increase in lymphocyte numbers than the patients who recurred suggesting that adaptive immunity plays a role in bladder cancer control.

Radiation in combination with checkpoint inhibitors (anti-CTLA4 or anti-PD1/PDL1 antibodies) appears to be a promising approach [43] and is being explored in ongoing trials in urothelial cancer (Table 1). Pembrolizumab is a humanized

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Shaveta Mehta[a,b], *Tim Illidge*[a,b], *and Ananya Choudhury*[a,b]

RENAL CELL CARCINOMA

Preclinical studies documented over two decades ago that radiation could augment the systemic effect of interleukin-2 (IL-2) therapy [44]. Although these results were not replicated early clinical studies in metastatic renal cell cancer (RCC) with IL-2 along with radiotherapy [45,46]. Furthermore, there were emerging clinical evidences that dose given per fraction may be critical to unlock the synergy between radiation and immunotherapy [47]. Seung *et al.* [48] performed a pilot study merging stereotactic body radiation therapy (SBRT) and high-dose IL-2 in 12 patients with metastatic melanoma or renal cell carcinoma who had received no prior treatment for metastatic disease. A response rate (RR) of 67% was observed with combination treatment in comparison to 15% with IL-2 alone. Interestingly, a high frequency of proliferating $CD4^+$ effector memory T cells was noted in responding patients.

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Table 1. Ongoing trials of radiotherapy and immunotherapy in urological malignancies

Trial	Condition	Aim	Immunotherapy	Radiotherapy	Phase
NCT02621151	Muscle-invasive urothelial cancer of the bladder	To assess the efficacy of pembrolizumab (MK3475) added to concurrent radiation and gemcitabine in the management of patients with muscle-invasive urothelial cancer who are not candidates for or decline radical cystectomy.	Pembrolizumab	EBRT - 52 Gy in 20 fractions over 4 weeks (1 fraction = 2.6 Gy)	2
NCT02560636	Invasive bladder cancer, metastatic bladder cancer	To investigate the safety, tolerability and effectiveness of an immunotherapy drug called pembrolizumab used in combination with radiotherapy	Pembrolizumab	Hypofractionated radiotherapy	1
NCT01896271	Metastatic clear cell renal cell carcinoma	To evaluate the RR in patients with mRCC after treatment with HD IL-2 immediately following SABR to multiple metastatic sites	IL-2	stereotactic ablative body radiation therapy	2
NCT01884961	Metastatic renal cell cancer, metastatic malignant melanoma	Radiotherapy as an immunological booster in patients with metastatic melanoma or renal cell carcinoma treated with high-dose IL-2	High dose IL-2	Three daily doses boost radiotherapy at 6–12 Gy to at least 1, and up to a maximum of 5, metastatic fields	2
NCT02710253	Metastatic cancer	Salvage radiation therapy to induce systemic disease regression after progression on systemic immunotherapy	Any	Standard doses to 50 Gy in four fractions with stereotactic radiation or 30–45 Gy in 3–6 Gy fractions with conventional external beam radiation	2
NCT02086721	Oligometastatic solid tumours	Combining L19-IL2 with stereotactic ablative body radiotherapy in patients with oligometastatic solid tumour	L19-IL2	SABR, patients receive a schedule of 1× 30 Gy, 3× 15–20 Gy; 5× 12 Gy; 8× 7.5 Gy; to the 80% or 100% isodose.	1

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ABSCOPAL EFFECT

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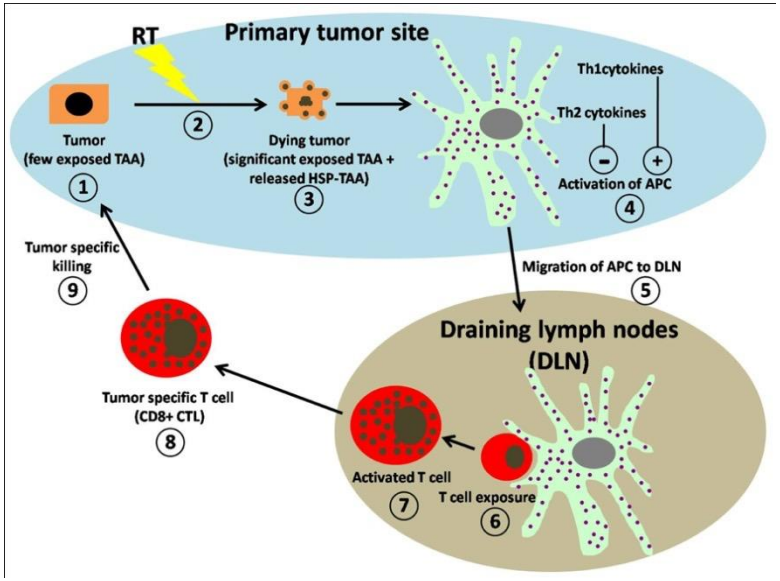
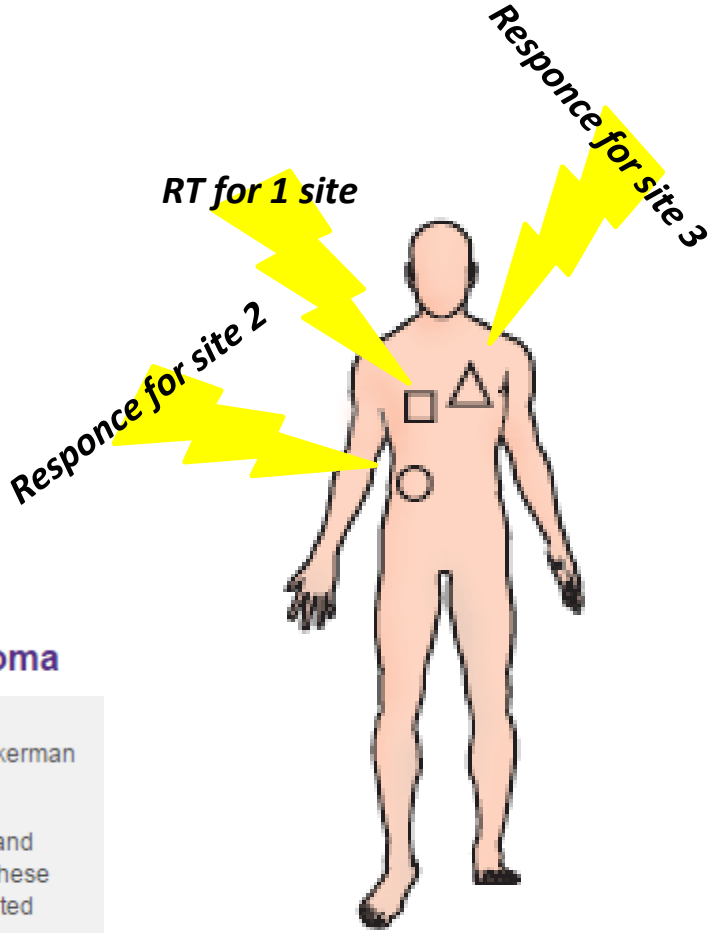
Immunotherapy and Radiotherapy

Abscopal Effect





An interesting case of possible abscopal effect in malignant melanoma

The natural history of malignant melanoma is notoriously unpredictable. Although long-term survival is not uncommon (Cade, 1961), lymph node involvement lowers the five-year survival rate to about 5 per cent (Ackerman and Del Regato, 1970).

It is generally accepted that radiation has no place in the treatment of metastases (Edwards, 1949; Kunkler and Rains, 1959) despite occasional reports of temporary tumour regression (Ellis, 1939; Sandeman, 1966). In these cases the response to irradiation occurred in the treated area and simultaneous regression of distant untreated metastases has never been reported.

Such behaviour has been given the term "abscopal effect". It occurs not uncommonly in leukaemia but is extremely rare in other tumours and the case reported below is therefore of interest.

Br J Radiol. 1975 Oct;48(574):863-6.

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ABSCOPAL EFFECT

There are a few proof-of-principle trials reported with local radiotherapy and granulocyte-macrophage-colony-stimulating factor (GM-CSF) to generate abscopal responses in patients with metastatic urological malignancies. Formenti *et al.* [49] reported an encouraging 30% abscopal response in a study of 14 patients with advanced metastatic disease, including urothelial cancer that was treated with GM-CSF and received irradiation to one metastatic lesion at 35 Gy 10 fractions over 2 weeks. In another study, Golden *et al.* [22▪] reported the abscopal effect in 11 out of 41 patients with metastatic solid malignancies who received radiotherapy (35 Gy in 10 fractions over 2 weeks) along with GM-CSF. Wersall *et al.* [47] showed regression of

Immunotherapy and Radiotherapy and Renal & Bladder cancer

Regression of non-irradiated metastases after extracranial stereotactic radiotherapy in metastatic renal cell carcinoma

Acta Oncologica, 2006; 45: 493–497

Peter J. Wersäll, Henric Blomgren, Pavel Pisa, Ingmar Lax, Karl-Mikael Kälkner & Christer Svedman

ABSCOPAL EFFECT

Stereotactic radiotherapy (SRT) has been used in our center for almost 15 years for treating inoperable primary tumors of renal cell carcinoma and metastatic lesions in various malignant diseases [3–6]. In 28 renal cell carcinoma patients with treated and untreated metastatic lesions, we have four cases where non-irradiated metastases have regressed temporarily or seemingly permanently after treatment with SRT of either the primary tumor or other metastatic lesions. The frequency of such responses

Immunotherapy and Radiotherapy and Renal & Bladder cancer

- ***Issues:***
- ***Timing***
- ***Dose***
- ***Toxicity***

The most important data about Immunotherapies are on «Melanoma patients»

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ABLATIVE SRS AND NEW DRUGS:

THE ISSUE

Systematic or Meta-analysis Studies

2017

Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: A systematic review

CrossMark

Stephanie G.C. Kroeze [a,*], Corinna Fritz [a], Morten Hoyer [b], Simon S. Lo [c], Umberto Ricardi [d], Arjun Sahgal [e], Rolf Stahel [f], Roger Stupp [f], Matthias Guckenberger [a]

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[c] Department of Radiation Oncology, University of Washington School of Medicine, 1959 N.E. Pacific Street, Box 356043, Seattle, USA
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- *…a reconsideration of previous dogmas related to the combination of target systemic and local therapies (including SABR) is now recommended.*
- *Interactions between conventional RT and targeted agents are reasonable well understood ad toxicity data are available in literature.*
- *SABR cause vascular damage, immuno-influences have been reported…consequently different radio-biology might result in* ***unexpected interactions and toxicity profiles****.*

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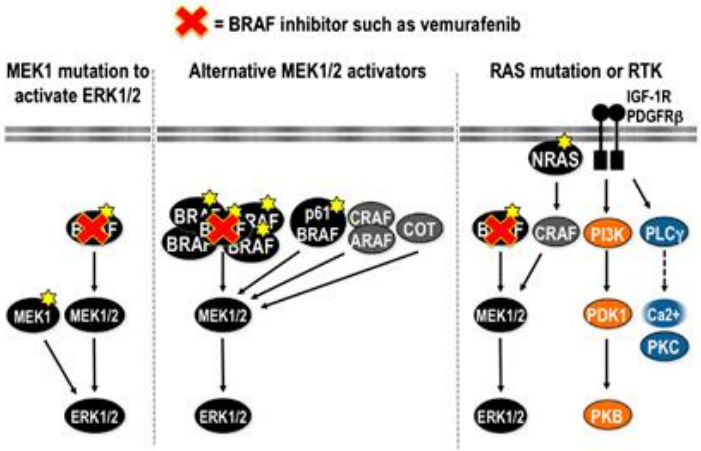
- *In conclusion,* ***cranial SRT is well tolerated when combined with the majority of targeted drugs and immune-therapies*** *but the combination with BRAF-Inhibitors should be practiced with caution.*



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Immunotherapies and Radiotherapy

Future Direction

Int J Radiation Oncol Biol Phys, Vol. 95, No. 4, pp. 1254–1256, 2016

Table 1 Overview of ongoing clinical trials combining RT with IT

	Vaccination	CTLA-4	PD-1	Others*	Total
Estimated enrollment	3310	692	692	667	5252†
No. of trials	30	20	15	18	81†
No. primarily sponsored by industry‡	15	0	2	1	18
Phase					
0	0	1	1	2	4
1	9	9	7	3	26†
1/2	1	3	2	8	14
2	16	7	5	5	32†
3	4	0	0	0	4
Cancer type					
Breast	1	0	1	6	8
GBM	5	0	1	0	6
Melanoma	1	14	2	1	17†
NSCLC	2	1	4	1	7
Pancreatic	9	1	2	1	12†
Prostate	6	0	0	1	7
Others	6	4	6	9	25
Dose per fraction§					
0-2.9 Gy	22	3	6	2	33
3-5.9 Gy	4	3	0	2	9
6-10 Gy	5	10	8	9	31
>10 Gy	2	7	1	7	17
Fractionation§					
1 fraction	4	5	2	5	16
2-5 fractions	6	11	7	14	38
6-10 fractions	0	3	0	3	6
10-27 fractions	0	0	0	0	0
>27 fractions	22	1	6	1	30
RT timing§					
RT >1 wk before IT	9	5	3	0	17
RT within 1 wk of IT	9	10	7	12	38
RT >1 wk after IT	7	4	3	4	18

Immunotherapy and Radiotherapy and Renal & Bladder cancer

Conclusion

- ***Preclinical models and clinical data showed that RT to one or few metastases might trigger and/or enhance the so called abscopal effect.***
- *RT can augment response to immunotherapy in urological malignancies.*
- ***This effect is amplified when RT is combining with Immunotherapy, including anti-CTLA-4 or anti-PD-1/anti-PDL1 antibodies.***
- ***Limited evidence in urological malignancies*** *but studies are on-going to address issues around combination of RT-immunotherapy*. ***Several prospective trials are ongoing to define which is the best combination strategy (timing), as well the best RT dose/fractionation regimen.***

Curr Opin Urol 2016, 26:514–522

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THANK YOU….