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The abscopal effect of local radiotherapy: using immunotherapy to make a rare event clinically relevant

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Abstract

Background—Recently, immunologic responses to localized irradiation are proposed as mediator of systemic effects after localized radiotherapy (called the abscopal effect). Here, we give an overview of both preclinical and clinical data about the abscopal effect in particular and link them with the immunogenic properties of radiotherapy.

Methods—We searched Medline and Embase with the search term “abscopal” from 1960 until July, 2014. Only papers that cover radiotherapy in an oncological setting were selected and only if no concurrent cytotoxic treatment was given. Targeted immune therapy was allowed.

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Results—Twenty-three case reports, one retrospective study and 13 preclinical papers were selected. Eleven preclinical papers used a combination of immune modification and radiotherapy to achieve abscopal effects. Patient age range (28 to 83 years) and radiation dose (median total dose 32 Gy) varied. Fractionation size ranged from 1,2 Gy to 26 Gy. Time to documented abscopal response ranged between less than one and 24 months, with a median reported time of 5 months. Once an abscopal response was achieved, a median time of 13 months went by before disease progression occurred or the reported follow-up ended (range 3–39 months).

Conclusion—Preclinical data points heavily towards a strong synergy between radiotherapy and immune treatments. Recent case reports already illustrate that such a systemic effect of radiotherapy is possible when enhanced by targeted immune treatments. However, several issues concerning dosage, timing, patient selection and toxicity need to be resolved before the abscopal effect can become clinically relevant.

Keywords

irradiation; abscopal effect; radiotherapy; immune therapy

Introduction

Radiotherapy (RT) is highly effective anticancer treatment leading to local tumor control and potential cure for early stage cancer. Targeted ionizing irradiation has long been known to cause direct localized cell death. However, irradiation is also increasingly recognized to be able to induce tumor regression at non-irradiated, distant tumor sites. This phenomenon is called the “abscopal effect”, a term first introduced by Mole in 1953 and later on broadened by Andrews to include distant normal tissue effects [1, 2]. The existence of this type of effect is mainly described in sporadic case reports. Because documented abscopal regressions are rare, its clinical relevance is uncertain with current routinely used radiotherapy regimens. Nevertheless, recent insights regarding the immunogenic effects of RT and the biological mechanisms of the abscopal effect have provided renewed interest in the ability of radiotherapy to induce distant tumor regression leading to meaningful clinical benefit. The immune system has been proposed as the key component of abscopal effects after radiotherapy [3]. Local radiotherapy is known to induce an immunostimulatory form of cell death, called immunogenic cell death (ICD), leading to host immune responses [4–7]. The concept of ICD relies mainly on the release of damage associated molecular patterns (DAMPs) which trigger an antigen engulfment of dendritic cells (DC). This subsequently results in an improved antigen presentation to the cytotoxic immune system [8, 9] (see figure 1). Irradiation is also known to alter the immune phenotype of the tumor by augmenting the presence of MHC I on the tumor cell surface, improving expression of cancer-testis antigens and upregulating the FAS/CD95 complex [10–13]. Furthermore, RT is recognized to create a cytokine pattern that facilitates migration and function of effector CD8⁺ T cells [14, 15]. Therefore improved antigen expression and presentation as well as enhanced functioning of effector T cells provide a sound potential rationale for an immune mediated abscopal effect.

Here we overview the current state of knowledge of preclinical data and clinical experience regarding the abscopal effect. The aim of this review is to provide a systematic overview of the abscopal effect and identify links with the immunogenic properties of radiotherapy.

Finally, we critically assess future therapeutic possibilities of radiotherapy in combination with the large number of emerging immunomodulatory agents [16].

Search strategy and selection criteria

References for this review were identified through searches of Medline and Embase with the broad search terms “abscopal”, “(non-targeted irradiation) OR (non-targeted radiotherapy)” and “distant bystander” from 1960 until July, 2014. Title and abstracts were screened by the main author and papers that were selected were verified by the other authors. English, Dutch and French clinical papers were included if they met the following criteria: patients had to receive single or multiple fractions of radiotherapy for any malignancy. Following radiotherapy, a non-irradiated tumor site needed to show size and/or metabolic regression. Biopsy confirmation of a responding distant site was not mandatory as clinical practice does not routinely require it. Papers were not considered eligible if whole body irradiation was used or if concurrent systemic treatment with a cytotoxic drug was given. Sequential cytotoxic treatment after radiotherapy was not allowed unless an abscopal radiotherapy response was assessed before the following systemic treatment was given. Concurrent or sequential immune modifying therapy was included though handled separately from radiotherapy-only cases.

For preclinical research relevant to an abscopal effect, the final reference list needed to focus on abscopal effects in the oncological setting. Therefore, only *in vivo* studies that concerned a malignancy were selected as *in vitro* models are mostly confined to study short-range bystander effects. Distant tumor regression was an essential endpoint. Combinations of immune modifying agents and radiotherapy were included. Concurrent treatment with a cytotoxic drug was not allowed.

References of selected clinical and preclinical papers were also screened for additional papers that met our selection criteria.

Results

Using the described methodology, we identified 378 Medline and 555 Embase references in total (figure 2). Thirteen preclinical papers were retrieved that directly identified abscopal effects *in vivo*, which are summarized in table 1. Eleven of these studies used radiotherapy in conjunction with an immune treatment to achieve an abscopal effect. Out of the 5 different mouse models, BALB/C and C57BL/6 were by far the most used (6 times each). Dose varied extensively, ranging from one fraction of 2 Gy to 3–5 fractions of 10 Gy and even high dose single fractions of 60 Gy.

One retrospective clinical study was retrieved. No randomized clinical studies were identified. A total of 25 case reports were initially eligible, all based on one or more clinical cases, but two of those case reports which described 12 individual clinical cases were additionally rejected due to insufficient clinical information [17, 18]. Thus, we ultimately retrieved 23 case reports of a perceived abscopal effect through radiation therapy with or without immune therapy. These are summarized in table 2 and 3 respectively. Patient age ranged from 28 to 83 years, with a median age of 64.5. Interestingly, renal cell carcinoma

was the most frequent histology in the group without immune therapy, with 7 cases, followed by 4 cases of hepatocellular carcinoma. Radiation doses varied as well, with a median total dose of 32 Gy (range 12 Gy – 60,75 Gy). Fractionation size ranged from 1,2 Gy to 26 Gy. Eight cases were irradiated on the primary tumor site, 14 on a distant metastatic or nodal site. Time to documented abscopal response ranged between less than one and 24 months, with a median reported time of 5 months. Once an abscopal response was achieved, a median time of 13 months went by before disease progression occurred or the reported follow-up ended (range 3–39 months). In 11 case reports the progressive free survival time could not be assessed.

Discussion

The effector T cell response is crucial for abscopal effects

Preclinical studies investigating the abscopal effect are relatively immature. As one of the first to demonstrate an abscopal effect in vivo, Chakravarty *et al.* set up a metastatic Lewis lung carcinoma (LLC) model in the feet of mice and irradiated only one tumor localization with a single dose of 60 Gy. Subsequently, this group administered Fms-like tyrosine kinase receptor 3 ligand (Flt3-L), a growth factor for dendritic cells (DC)[19]. Combination treatment improved disease-free survival at 20 weeks by 56% and reduced non-irradiated pulmonary metastasis (evaluated by mean lung weight) on multiple sites compared to monotherapy of either RT or Flt3-L. The addition of improved dendritic cell growth to the enhanced antigen processing and presentation of RT lead to a systemic response in this setting. Additionally, the abscopal effect was lost in athymic mice, indicating the potential importance of T cell presence in the host. In a follow-up study, increased levels of IL-12, IFN- γ and IL-2 also point to a pro cytotoxic T cell pattern as the driver behind systemic tumor regression [20]. This synergy between RT and Flt3-L and the importance of proper T cell functioning was confirmed in a poorly immunogenic mammary carcinoma model (67NR) by Demaria *et al.* [21].

Furthermore, Yasuda *et al.* used IL-2 injections to successfully reach an abscopal effect [22]. IL-2 - already described as an important driver for an abscopal effect by Chakravarty *et al.* - is a stimulator of effector T cells and was administered after irradiating an established subcutaneous colon26 tumor (10x 2 Gy). Thus, a systemic response was achieved not by increasing antigen presentation through DC manipulation, but by enhancing the function of the T cells in a more direct manner. Shiraishi *et al.* used ECI301, a macrophage inflammatory protein 1 α (MIP-1 α) variant, as a tool to create a more tumoricide environment [23]. MIP-1 α is secreted by various leukocytes and recruits monocytes, dendritic cells, NK cells and T cells. Only combination treatment showed a reduction in tumor growth at the non-irradiated side. Irradiation of the normal tissue in the hind flank in combination with ECI301 did not elicit an abscopal effect. When looking at T cell infiltration, irradiation with ECI301 caused increased CD4+ and CD8+ populations in both irradiated and non-irradiated tumors. This was not observed with ECI301 or RT alone and depletion of these cell populations abrogated the abscopal effect completely. Although most of these drugs did not impact standard clinical treatments, they do illustrate that the synergy between radiotherapy and immune treatment enables a strong systemic effect. This systemic

effect relies upon a broad T cell foundation, inclusive of a functional system ranging from antigen presentation to effector T cell response. The multitude of experimental drugs that are capable of enhancing such a T cell response indicates a lot of potential to unlock consistent abscopal effects in clinical practice.

Targeted immune therapy opens the door for synergistic combination treatments

In recent years, the emergence of immunotherapies in a clinical setting is opening up new opportunities to elicit abscopal effects. Demaria *et al.* illustrated this potential with an experiment that combined cytotoxic lymphocyte antigen-4 blockade (CTLA-4) with irradiation [24]. Combination treatment of RT and CTLA-4 blockade did result in a significant survival improvement over the monotherapy and control groups. CTLA-4 is a checkpoint mechanism that regulates the immune system and prevents overstimulation and resultant autoimmunity. CTLA-4 is a key molecule for regulatory T cells in this regard. CTLA-4 blockade is widely accepted as an effective approach in malignant melanoma and is a prime candidate for other cancer treatments as well [25]. This correlated with the impairment of lung metastases formation as an abscopal effect. Through depletion experiments they also displayed that the presence of CD8+ T cells was crucial in obtaining such a result.

Deng *et al.* investigated the role of potential synergistic RT-immunotherapy regimens to anti-PD-L1 [26]. PD-L1 (programmed death-ligand 1) is an important player in inhibiting a proficient T cell response. Besides from an increase in PD-L1 expression in the tumor microenvironment after a single dose of 12 Gy, they showed a growth reduction at the non-irradiated site when combination therapy was administered.

In summary these *in vivo* studies emphasize the rarity of abscopal effects in the setting radiotherapy alone without additional immunomodulation, in keeping with the published clinical case reports. In contrast, the preclinical data provide encouraging results for a variety of immunomodulatory agents which may synergize with radiotherapy to induce durable systemic anti-tumor immune responses, providing support to translate such findings to the clinic.

Frequency of clinical abscopal effects is dependent on tumor type and follow-up

Clinical cases of abscopal effects in response to radiotherapy have been reported since 1973. Nevertheless, there have only been a limited number of clear-cut systemic responses identified in the last forty years. Preclinical research also fails to consistently reproduce abscopal effect by RT alone. Nevertheless, the clinical case reports illustrate a number of important aspects that might influence the presence of these abscopal effects. When reviewing the case reports, an immediate observation is the striking feature of the abscopal effects occurring in immunologically prominent tumor types such as RCC, melanoma and HCC. In this context, it is remarkable that these are frequently associated with spontaneous regression as well [27]. One could argue that the abscopal effect actually is a coincidental representation of spontaneous regression. The inflammatory microenvironment and the cytotoxic immune system have been suggested as the main drivers of spontaneous regression [28–30]. However, the aforementioned preclinical data shows a strong T cell dependence in

response to inflammatory radiation stimulus when documenting abscopal effects as well. Thus, it is not surprising that abscopal effects as well as spontaneous regression are more prevalent in two tumor types that are recognized for having a more established immunogenicity. Distinguishing abscopal effects from spontaneous regression is not straightforward, which might lead to underreporting.

Recognizing true abscopal effects is particularly challenging in the setting of a hematological malignancy. It is reported that circulating neoplastic lymphocytes that pass through the irradiated field could account for gradual cell depletion/death of the total circulating lymphocyte pool and mimic an abscopal effect due to lymph node reduction [31]. Identification of the abscopal effect is limited by the scheduled restaging imaging too. Both the restaging method and its timing impact the perceived presence and extent of an abscopal effect. Some case reports describe solely clinical regression or only performed partial disease imaging. Moreover, after palliative radiotherapy, there is often a loss of follow-up or second or third line systemic treatment is immediately started. This masks potential distant disease regression due to an adaptive immune response. To completely assess abscopal effects a full picture of the disease evolution should be made on regular time intervals while recognizing confounders such as sequential chemotherapy.

The difference in immunogenic potential between tumor types and probably between individuals should be taken into account when developing trials that study the immunogenic potential of radiotherapy. Although abscopal effects are more often missed rather than recognized due to the aforementioned reasons, it still remains a rare phenomenon. To apply irradiation in an immunogenic setting, additional therapeutics need to be considered.

Abscopal effects after clinical combination treatments

The immunologic potential of certain tumors also comes forward in the multiple case reports that describe combination treatment of RT and immunotherapy. A number of manuscripts have confirmed the presence of an abscopal effect of radiotherapy in combination with an immunomodulating agent. Four case reports with ipilimumab and one with BCG-vaccination are summarized in table 3. Only one retrospective study was performed, about the sequence ipilimumab-radiotherapy in 21 patients with melanoma [32]. They were considered eligible when they showed progressive disease after ipilimumab (3-weekly, 3 mg/kg) and received palliative radiotherapy afterwards. Eleven patients (52%) showed an abscopal response after RT, two of which had stable disease for >3 months instead of a distant partial or complete response. Time to abscopal response ranged from 1 to 4 months. Median overall survival increased to 13 months, which differed significantly from the patients without an abscopal response. Although retrospective, this data really complements the findings of the case reports. Not surprisingly, malignant melanoma was chosen to investigate as it is one of the cancers that act on the forefront of immunotherapy studies. Response time is typically several months after irradiation, which fits with a cellular immune response. An important aspect of this study is that it consisted of sequential therapy rather than concurrent. Concurrent success is illustrated by Golden *et al.*, who administered 4 three-weekly cycles of ipilimumab (3mg/kg) for lung adenocarcinoma [33]. The first cycle was initiated one day after starting the radiotherapy schedule (6 fractions of 5Gy). Hiniker *et*

al. also prospectively combined stereotactic radiotherapy (54 Gy in 3 fractions) with ipilimumab, this time in a metastatic melanoma patient [34]. Postow *et al.* reported that their patient received 4 cycles of induction ipilimumab (10mg/kg) for malignant melanoma after which maintenance treatment was started twelve-weekly (dose not specified)[35]. After more than one year of maintenance treatment with slightly progressive disease, palliative radiotherapy was started (28,5 Gy in 3 fractions). One month later one more cycle of ipilimumab was given which resulted in a subsequent abscopal response. Stamell *et al.* reported an abscopal effect after combining ipilimumab with stereotactic radiotherapy in a melanoma patient [36].

Ipilimumab is currently the most used immune agent available. It causes CTLA-4 blockade which leads to a decreased regulatory T cell activity. It synergizes well with RT since regulatory T cells lead to a suppressed immune response and tend to be more radioresistant than other T cells [37]. Both preclinical data and clinical case reports strongly hint towards CTLA-4 blockade as a prime candidate for combination treatments. However, the wide array of successfully applied drugs in preclinical models also suggests a broad synergistic potential of other drugs. Promising clinical immune agents like PD-1/PD-L1 blockade should therefore be explored in combination with radiotherapy as well.

In sequential therapy, it may be challenging to delineate the abscopal contribution from radiation therapy with delayed immunotherapeutic response. When concurrent RT and immune therapy is applied, it is impossible to distinguish an abscopal effect from a pure drug effect. To make a qualitative assessment of relative contributions of effect, biomarkers for an RT induced immune response are much needed. Assessing the scale of the abscopal effect when combined with immune therapy is beyond the scope of the present review. Future clinical trials with rigorous investigation of sequence and timing of radiotherapy and immunotherapy combinations are best placed to determine the relative activity of each treatment modality.

Unraveling molecular mechanisms

Although hard endpoints are to be prioritized when evaluating abscopal responses, the importance of the underlying molecular mechanisms should not be underestimated. Knowledge of significantly related circulating proteins is vital for the development of biomarkers and potentially able to open up new therapeutic approaches. With the exception of immunogenic cell death, this is still largely unexplored terrain. Two preclinical models suggest p53 as a key mediator for abscopal effects [38, 39]. In clinical research, a couple of the mentioned papers also explored individual markers in abscopal responses. Postow *et al.* explored the presence of NY-ESO-1 antibodies after radiotherapy. NY-ESO-1 is a prime example of a cancer-testis antigen and a high antibody titer increases the efficiency of ipilimumab [40]. That titer turned out to be 30 times higher after radiotherapy than before. Additionally, they also observed a supplemental increase of CD4+ T cells after RT, and a decrease in myeloid-derived suppressor cells right before an abscopal regression was identified. Titers against melanoma antigen-A3 rose significantly after irradiation and ipilimumab as well.

A more cytokine focused approach was used by Ohba *et al.* In a patient with metastasized hepatocellular carcinoma, they performed serial measurements of serum cytokines before and after radiotherapy [41]. An abscopal regression occurred together with a decrease in AFP. More importantly, they also displayed an increase of TNF- α after RT. TNF- α is capable of inducing cell death and activate natural killer cells and thus applied in several experimental regimens as a cancer treatment [42]. In contrast, Nakanishi *et al.* performed the same cytokine panel, also in a patient with HCC, but without a notable increase in TNF- α [43]. They did note a rise in IL-18 both before and after radiotherapy.

The current occasional explorative testing for molecular mechanisms is able to suggest, but not to conclude. Implementing a thorough molecular approach in clinical trials is important for biomarker development and obtaining more insight in the molecular pathways that form the foundation of an adaptive antitumor immune response.

Time & dose are of the essence

Since an abscopal response is dependent on cytotoxic immunity, it is expected that several weeks to months need to pass before an adequate assessment can be made. The clinical data suggests that indeed a time frame of several months is needed before a clinical response can be detected. As an indirect indicator of an adaptive immune response, there is a notable similarity with ipilimumab. It is suggested that clinicians should not terminate treatment with ipilimumab prematurely since there is an important variance in time to response [44]. Once disease progression is halted, it usually can maintain this state for a very long time, which the case reports of abscopal effect indicate as well. A cytotoxic T cell based anti-tumor effect fits this pattern perfectly. A closely related aspect is the close timing of radiotherapy and immune modifying agents in preclinical mouse work. The theoretical concept of ICD and improved immunogenicity through irradiation supports the concept that a concurrent administration of radiotherapy and immune modifying agents is superior to sequential treatments. The preclinical work indicates that separating RT and immune modification in time reduces the therapeutic efficacy. This should be confirmed clinically. But even then, a lot of questions remain. Is this a one-shot treatment or does repeated exposition to irradiation throughout immunotherapy bring additional benefit? Such a repeated approach could be thought of as booster treatments, in analogy with vaccination schedules. On top of that, if systemic immunity needs a median of 4 months to attend a beneficial effect, it might be opportune to continue immune treatments for at least 4–6 months.

Closely related to the timing of both therapy components is the irradiation schedule that is applied. Most preclinical data today uses high dose, low fractionated radiotherapy, although this is only holds limited clinical appeal. The importance of RT scheduling is also hinted at by Dovedi *et al.* They showed that the combination of RT and anti-PD-L1 may overcome RT induced adaptive resistance by upregulation of PD-L1 [45]. This upregulation of PD-L1 occurs with fractionated RT. The article illustrates that incorporating radiobiological differences of varying fractionation and dose is crucial to keep a translational perspective. Efficacy of drug-RT combinations can change when dose and fractionation change.

Limits of current study design

There are several limitations to the current clinical and preclinical data that need to be pointed out. Radiographic evaluation was often not described well in the case reports. A one-dimensional and/or volumetric response assessment is implied in most case reports, but often without any detailed information regarding effect size. Additionally, the time point and method of tumor assessment are often arbitrary, which is an important facet since they often determine the ‘appearance’ and validity of an abscopal effect. Another important issue is the translational validity of preclinical mouse work. Tumor immune phenotype is extremely important and highly variable in a clinical setting, which begs the question if strict mouse models represent suitable circumstances for an abscopal effect based on irradiation alone. Moreover, the number of preclinical studies is limited and varies in set-up and methodology. This can definitely be extended towards parameters like total dose, dose fractionation and timing as discussed. If substantial progress is to be made, they need to be addressed.

Horizon scanning and future challenges

Irradiation should be regarded as an immunogenic hub to induce an in situ vaccination on which immunomodulatory agents can enhance systemic immune response. Conversely, many issues need to be addressed before radiotherapy can become such a valid immunogenic tool. Initiating clinical trials right now might yield success, but it also has the pitfall of quickly writing off a new therapeutic strategy because of poor study set-up. First and foremost, thorough knowledge about the relation between dose/fractionation and the immune effects of radiation is required. Preclinical and clinical work need to implement comparative regimens to establish optimal RT parameters. Changes in the structural tumor microenvironment that occur with different RT doses need to be taken into account. One example is the vascular disruption that occurs when ablative radiotherapy is given, which could alter drug delivery [46]. Additionally, timing of immune therapy with radiotherapy is crucial. It is probable that there is a window of opportunity that leads to an optimal synergy between RT and immune agents, which needs to be explored and defined. However, true concurrent regimens are not often applied in clinical trials because of fear of increased toxicity, which keeps preclinical work from reaching proper clinical implementation. The presumed increase in adverse effects when using concurrent radio- and immunotherapy has been doubted by a recent review by Barker *et al.* [47]. Further data on the safety of combining immune agents and radiotherapy is required.

Another area of increasing importance will be the development of suitable biomarkers that will be able to reliably assess ‘immunogenic tumor cell death’, immune effector stimulation and adaptive immunity. Such an immune profile of biomarkers will aid in searching for an optimal combination of radiotherapy and immunomodulation and allows for patient selection and response prediction. Preclinical models, although sometimes lacking in translational potential still form an important asset in guiding biomarker research.

Conclusion

In this review we conclude that an irradiation induced abscopal effect is based on antitumor immunity. Abscopal effects were observed at all ages, across a variety of tumor types and

with substantial differences in radiotherapy regimens and techniques. However, they do seem to occur more in known immunogenic tumor types. At the same time, the rarity of documented reports and the preclinical research suggest that abscopal effects induced by RT alone are unlikely to have major clinical impact on disease control in the context of metastatic disease. Preclinical data suggests that immune therapy synergizes with radiotherapy to enhance adaptive antitumor immunity and allow for systemic effects after irradiation, but attention needs to be given towards optimizing of dose regimens and timing, as well as patient selection through biomarkers. These are necessary steps to unlock a more efficient long term immune response after radiotherapy and make the abscopal effect clinically relevant.

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Highlights

- Current clinical and preclinical data of the abscopal effect is summarized.
- The abscopal effect is linked with the immunogenic properties of irradiation.
- Radiotherapy has a potential synergy with immune agents.
- The issues that come with combining radiotherapy and immune agents are addressed.

Figure 1. Immunogenic cell death

Endoplasmatic reticulum stress induced by radiotherapy leads to apoptotic release of DAMPs such as ATP (find-me signal) and membrane blebs with the CRT/ERp57 complex (eat-me signal).

Figure 2. Search results

Breakdown of the number of papers identified according to the search strategy and selection criteria.

Table 1

Overview of preclinical studies according to the search criteria.

Pub. Year	Ref.	Tumor type	Irradiated site/Dose	Immune therapy	Observed abscopal effect	Suggested mediator
2014	[26]	TUBO mammary/MCA38 colon	Flank/12 Gy	Anti-PD-L1	Distant tumor growth inhibition	CD8-lymphocytes
2014	[48]	FM3A mammary	Flank/6 Gy	ECI301	Distant tumor growth inhibition	HMGB1
2014	[38]	HCT116 colon	Flank/10–20 Gy	None	Distant tumor growth inhibition	p53
2011	[22]	Colon26	Flank/20 Gy	IL-2	Decreased no of hepatic M+	CD4-lymphocytes
2009	[49]	TSA mammary/MCA38 colon	Flank/20-24-30 Gy	9H10	Distant tumor growth inhibition	unknown
2008	[23]	Colon26/MethA sarcoma/LLC	Flank/6 Gy	ECI301	Distant tumor growth inhibition	CD4+/CD8+/NK-cells
2007	[50]	SCC VII	Femur/4–10 Gy	DC	Distant tumor growth inhibition	DC/gp96
2005	[24]	4T1 mammary	Flank/12–24 Gy	9H10	Distant tumor growth inhibition	CD8-lymphocytes
2004	[21]	67NR mammary	Flank/2–6 Gy	Flt3-L	Distant tumor growth inhibition	DC/T cells
2003	[39]	LCC/T241 fibrosarcoma	Hind leg/24–50 Gy	None	Distant tumor growth inhibition	p53
2003	[51]	D5 melanoma/MCA 205 sarcoma MethA	Flank/42,5 Gy	DC	Distant tumor growth inhibition	DC
2001	[52]	C3 cervical/sarcoma	Hind leg/30–50 Gy	DC	Distant tumor growth inhibition	DC
1999	[19]	LCC	Foot/60 Gy	Flt3-L	Lung M+ regression	DC

M+ = metastasis. LCC = Lewis Lung Carcinoma, DC = dendritic cells, SCC = squamous cell carcinoma.

Table 2

Clinical cases of abscopal effect after RT according to the search criteria.

Pub. Year	Ref.	♂ ♀	Age	Histology	Primary site	Treatment of primary	RT treated sites	RT Dose/ Fractions	Non-irradiated abscopal regression	Time to abscopal response	PFS after abscopal response #
2013	[53]	F	78	Adenocarcinoma	Lung	SRT	Primary	26 Gy/1x	Bone M+ Adrenal M+	12 m	3 m
2012	[54]	M	61	RCC	Kidney	Nephrectomy	Brain M+ Bone M+	18 Gy/1x 40 Gy/8x	Lung M+ Bone M+	1 m	33 m
2012	[55]	M	72	Medullary carcinoma	Thyroid	Thyroidectomy	LN 4R (mediastinal)	30 Gy/3x	LN 6 (mediastinal)	1m	NR
2011	[56]	M	63	HCC	Liver	Hepatic Lobectomy	Mediastinal LN	60,75 Gy/27x	Lung M+	1 m	36 m
2011	[57]	M	70	Merkel cell carcinoma	Calf	Excision + adjuvant EBRT	In-transit cutaneous M+	12 Gy/2x	Other cutaneous M+	1 m	25 m
2009	[58]	F	65	Lymphocytic leukemia	Axillar LN	CT (PD)	Axillar LN	24 Gy/12x	Cervical LN	1 m	6 m
2008	[43]	M	79	HCC **	Liver	Embolization one lesion	VCI invasive lesion	48 Gy/NR	Hepatic sites	5 m	NR
2007	[59]	F	69	SCC	Cervix	EBRT Brachytherapy	Primary tumor	50,8 Gy/27x 24 Gy/4x	Para-aortic LN	NR	NR
2006	[60]	F	83	RCC **	Kidney	SRT	Primary tumor	32 Gy/4x	Lung M+ Abdominal LN	24 m	NR
2006	[60]	F	64	RCC	Kidney	Nephrectomy	Lung M+	NR	Lung M+	5 m	NR
2006	[60]	M	69	RCC	Kidney	Nephrectomy	Lung M+	30 Gy/2x	Lung M+	3 m	8 m
2006	[60]	F	55	RCC	Kidney	SRT	Primary tumor	32 Gy/4x	Abdominal LN+	5 m	NR
2005	[61]	M	65	HCC	Liver	None	Bone M+	30 Gy/NR	Hepatic sites Bone M+	10 m	13 m
1998	[41]	M	76	HCC	Liver	Resection/Embolization/CT (PD)	Bone M+	36 Gy/NR	Hepatic sites Bone M+	10 m	29 m
1995	[62]	M	77	CLL	/	CT (PD)	Neck/supraclavicular LN	32,4 Gy/NR	Peripheral LC Splenomegaly	1 m	NR
1994	[63]	M	58	RCC	Kidney	EBRT	Primary tumor	20 Gy/10x	Lung M+ Mediastinal LN	6 m	11 m
1983	[64]	M	49	Adenocarcinoma	Oesophagus	EBRT	Primary tumor	40 Gy/20x	Lung M+	6 m	13 m
1983	[64]	M	56	Adenocarcinoma	Lung	EBRT	Primary tumor	35 Gy/10x	Cutaneous M+	1 m	6 m
1981	[65]	F	73	RCC	Kidney	Nephrectomy	Groin M+	40 Gy/15x	Lung M+	12 m	39 m
1977	[66]	M	44	Lymphocytic lymphoma	LN	EBRT	Mantle field	30 Gy/20x	Abdominal LN	1 m	NR
1977	[66]	M	40	Lymphocytic lymphoma	LN	EBRT	Mantle field	30 Gy/20x	Abdominal LN	1 m	NR

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Pub. Year	Ref.	♂ ♀	Age	Histology	Primary site	Treatment of primary	RT treated sites	RT Dose/ Fractions	Non-irradiated abscopal regression	Time to abscopal response	PFS after response*
1975	[67]	M	28	Melanoma	Knee	Wide excision	Right inguinal LN	14,4 Gy/12x	Para-aortic LN	2 m	17 m
1973	[68]	F	35	Adenocarcinoma	CUP	/	Neck/Supra-clavicular LN	40 Gy/20x	Mediastinal mass	NR	NR

PFS = progressive free survival, M = male, F = Female, EBRT = external beam radiotherapy, CT = chemotherapy, RCC = renal cell carcinoma, M+ = metastasis, HCC = hepatocellular carcinoma, LN = lymph node(s), PD = progressive disease, VCI = vena cava inferior, SCC = squamous cell carcinoma, SRT = stereotactic radiation therapy, CLL= chronic lymphocytic leukemia, LC = lymphocytes, CUP = cancer of unknown primary, NR = not reported, / = not applicable.

* This indicates the time period that went by from the observation of abscopal regression until progressive disease OR until reported follow-up ended.

** No pathological diagnosis was reported. Tentative diagnosis based on imaging and disease presentation.

Table 3

Clinical cases of abscopal effect after RT + immune therapy.

Pub. Year	Ref.	♂ ♀	Age	Histology	Primary site	Treatment of primary	RT treated sites	Treatment + RT Dose/fractions	Non-irradiated abscopal regression	Time until abscopal response	PFS after response*
2014	[69]	M	74	Adenocarcinoma	Lung	Resection	Supraclavicular LN	BCG-vaccine 58 Gy/29x	Lung M+	6 m	47 m
2013	[33]	M	64	Adenocarcinoma	Lung	CT (PD)	Hepatic M+	Ipilimumab 30 Gy/5x	Liver M+/Bone M+/Lung M+	3 m	5 m
2012	[34]	M	57	Melanoma	Arm	Wide excision/axillary dissection	Hepatic M+	Ipilimumab 54Gy/3x	Cutaneous M+	6 m	6 m
2012	[36]	M	67	Melanoma	Scalp	CT (PD)	Brain M+	Ipilimumab SRT**	Nodal M+	NR	NR
2012	[35]	F	33	Melanoma	Upper back	Wide excision	Paraspinal M+	Ipilimumab 28,5 Gy/3x	Splenic M+/hilar LN	4 m	6 m

PFS = progressive free survival, M = male, F = Female, M+ = metastasis, LN = lymph node(s), EBRT = external beam radiotherapy, CT = chemotherapy, PD = progressive disease, SRT = stereotactic radiation therapy.

* This indicates the time period that went by from the observation of abscopal regression until progressive disease OR until reported follow-up ended.

** Total dose and fractionation not reported.