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Critical Review

A Patient-Level Data Meta-analysis of the Abscopal Effect

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Abstract

Purpose: The abscopal effect is defined when a form of local therapy causes tumor regression of both the target lesion and any untreated tumors. Herein cases of the abscopal effect were systematically reviewed and a patient-level data analysis was performed for clinical predictors of both duration of response and survival.

Methods and Materials: The Population, Intervention, Control, Outcome, Study (PICOS) design approach, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process, and Meta-analysis of Observational Studies in Epidemiology (MOOSE) were used to find articles published before September 2019 in MEDLINE/PubMed and Google Scholar. Inclusion criteria were (1) population: patients with reported abscopal response; (2) intervention: documented treatment(s); (3) control: none; (4) outcomes: overall and progression-free survival; and (5) setting: retrospective case reports. Time from treatment until abscopal response and time from abscopal response until progression/death were calculated. Univariate and multivariate analyses were conducted for survival outcomes.

Results: Fifty studies (n = 55 patients) were included. Median age was 65 years (interquartile range [IQR], 58-70) and 62% were male. Fifty-four (98%) patients received radiation therapy, 34 (62%) received radiation therapy alone, 5 (9.1%) underwent surgery, 4 (7.3%) received chemotherapy, and 11 (20%) received immunotherapy. Median total dose was 32 Gy (IQR, 25.5-48 Gy) and median dose per fraction was 3 Gy (IQR, 2-7.2). Median time until abscopal response was 4 months (IQR, 1-5; min 0.5, max 24). At 5 years, overall

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survival was 63% and distant progression-free survival was 45%. No variables had statistical significance in predicting duration of response or survival.
Conclusions: Almost all reported cases of the abscopal response are after radiation therapy; however, there are no known predictors of duration of response or survival in this population.

Introduction

The abscopal effect is defined when a form of local therapy (eg, radiation therapy [RT]) causes tumor regression of both the target lesion and any untreated tumors. Precise biological mechanisms are unknown, but the immune system may be integral in abscopal responses (Fig. 1).[1-3] Owing to promising preclinical data, interest exists in combining immunotherapy with hypofractionated RT to stimulate abscopal responses[4-7] and improve patient outcomes.[1,8-19]

Various mechanisms have been proposed to explain how radiation interacts with the immune system.[10-12,20] Synergistic RT and immunotherapy have been shown to promote local immune responses[4-7,13] and have been hypothesized to improve the probability of tumor control.[11] As a brief review, high dose per fraction RT has been shown to stimulate tumor associated antigen presentation and causes an increased ratio of immunologic cell death to tolerogenic responses, which stimulates CD8+ T lymphocytes, dendritic cells, and natural killer cells.[11] Immune checkpoint inhibitors prevent immune tolerance of tumor cells by blocking tumor cell escape from immune surveillance via cellular targets (ie, Programmed Cell Death-1 and Cytotoxic T-Lymphocyte Antigen-4), which are expressed by tumor suppressor cells (CD4+ T lymphocytes, CD8+ T lymphocytes, dendritic cells, and natural killer cells).[4-7,11,13] These synergistic effects were thought to prime the immune system and induce an abscopal response.

Previous systematic reviews have examined the abscopal effect[2,9]; however, data on progression-free survival, distant metastasis, and overall survival were not reported; use of systemic therapies (including immune checkpoint inhibitors) were not routinely mentioned; and analyses for predictors of response were not performed. The hypothesis was that certain clinical covariates might predict for survival of patients with an abscopal response. Thus, we performed the first patient-level data meta-analysis for predictors of response.

Methods and Materials

Literature selection

The Population, Intervention, Control, Outcome, Study (PICOS) design approach was used to define the inclusion criteria (Table 1). A systematic search was

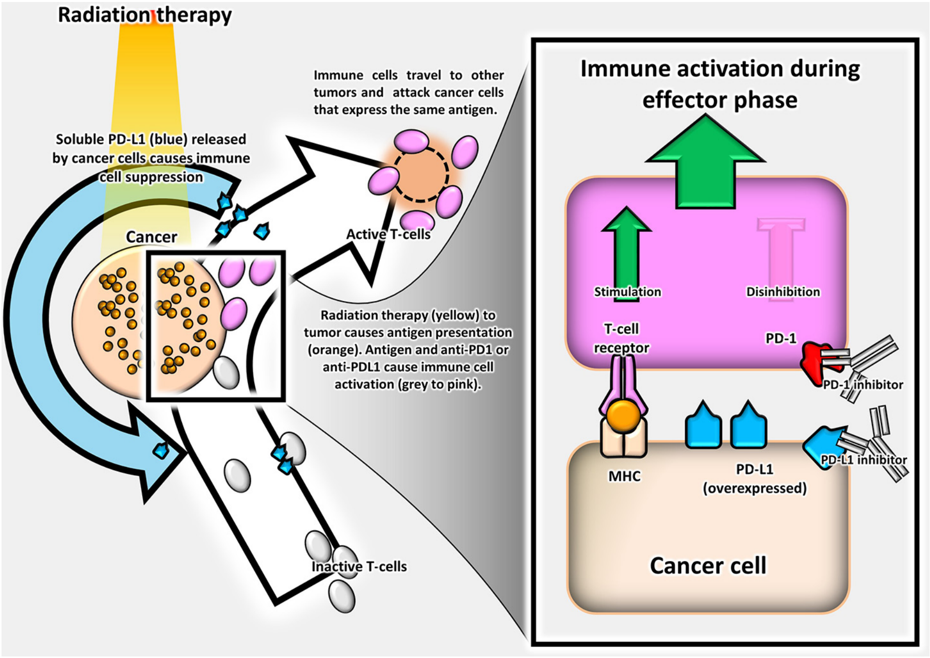

Figure 1 Abscopal effect defined.

Table 1 PICOS inclusion criteria

Population	Case reports of the abscopal effect published before September 26, 2019.
Intervention	Clearly defined cancer therapy at time of abscopal response and prior courses of treatment (eg, radiation therapy, immunotherapy, chemotherapy, target therapy).
Control	None.
Outcomes	Overall and progression-free survival. Time from treatment until abscopal response and time from abscopal response until progression or death were calculated. For overall and progression-free survival, the start time was calculated from the time of abscopal effect.
Study design	Case reports and case series published in the English literature.

Abbreviation: PICOS = Population, Intervention, Control, Outcome, Study.

performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) literature selection process (Fig. 2) of studies in MEDLINE (PubMed) and Google Scholar. Inclusion criteria were (1) population: patients with reported abscopal response, which was defined by any form of local therapy causing regression of both the target lesion and any untreated tumors; (2) intervention: documented treatment(s); (3) control: none; (4) outcomes: overall and progression-free survival; and (5) setting: retrospective case reports.

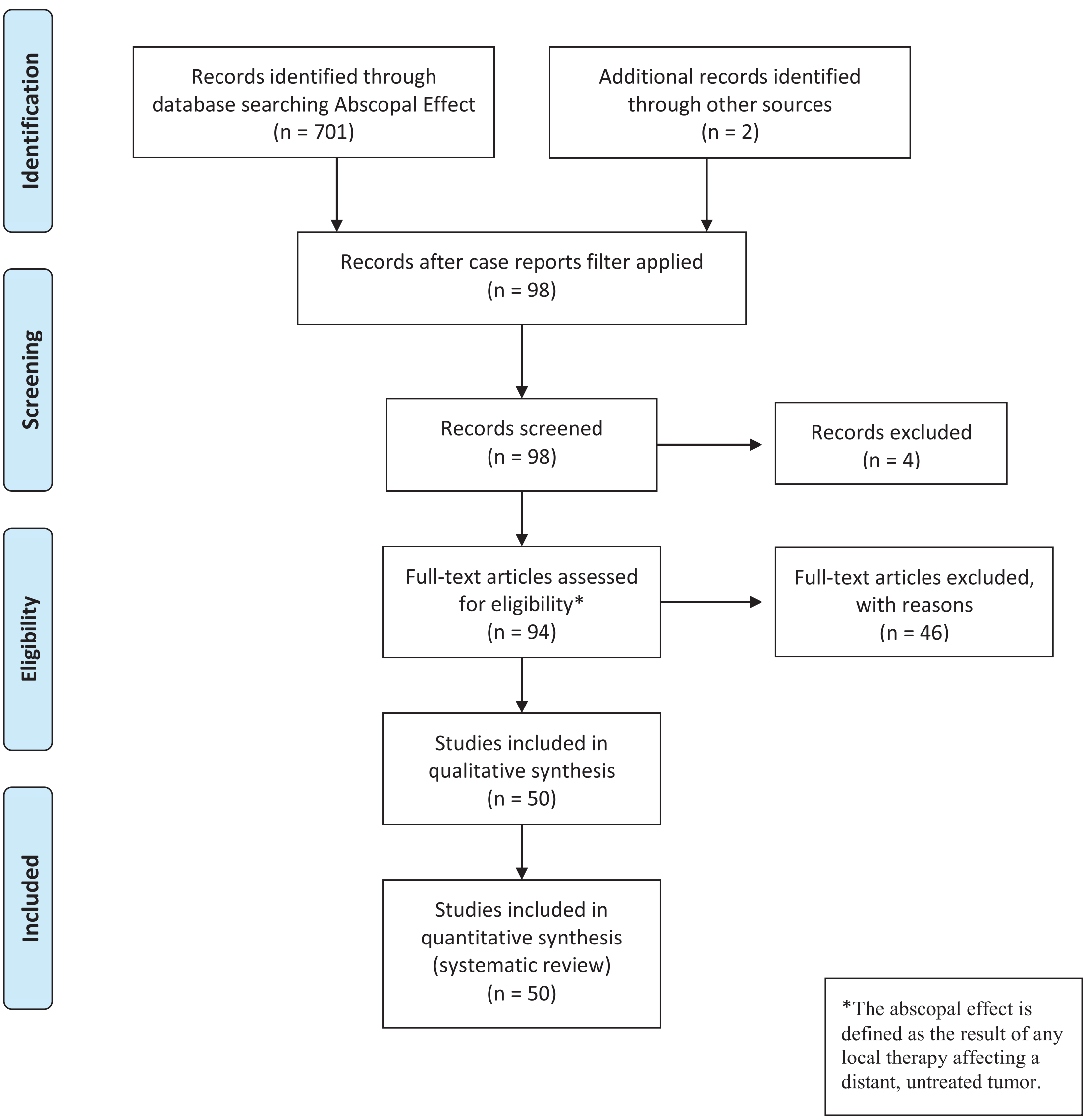

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

This method of a patient-level data meta-analysis has been described previously in the literature.[21,22] Relevant case reports were systematically identified through a search of PubMed/MEDLINE and Google Scholar with the broad term "abscopal effect." The initial search yielded 701 articles. Reports that were cited or linked from any review articles and the individual case reports were included. After identifying 98 articles, 4 were rejected because they were not case reports. The remaining articles were screened by the first author (S.J.H.) and were included based upon the aforementioned criteria. Patients could receive any combination of treatment: surgery, RT, immunotherapy, chemotherapy, or targeted therapy for any malignancy. Finally, 50 studies including 55 patients were included.

Data abstraction and analysis

The definition for the start time of an abscopal effect was marked by any regression at an untreated tumor site as noted by imaging, per the report of primary authors from each case report. Individual case reports were reviewed by authors and information was manually extracted and coded into a database. The following data were coded from each case report: characteristics about patients (ie, age, sex), cancer (ie, type [per National Comprehensive Cancer Network guidelines], histology, mutation, stage), treatments received at any point before an abscopal response (ie, surgery, radiation, chemotherapy, immunotherapy), radiation dose (ie, Gy, dose/Gy, biologically effective dose with an α/β of 10), treatment received during the abscopal response (eg, radiation, chemotherapy, immunotherapy, target therapy), time from radiation to an abscopal effect, interval of follow- up/recurrence, and outcomes (ie, overall survival and distant progression-free survival at last known contact date). Unknown/missing variables were coded as missing in the database.

Results

The data of both patient and cancer characteristics are in Table 2. Fifty studies (n = 55 patients) published from 1954 to 2019 met inclusion criteria and were used.[23-76] The median patient age was 65 years (interquartile range [IQR], 57-70), and there were 34 (62%) men and 21 (38%) women. Although all patients had metastatic disease at the time of the abscopal effect, only 17 (31%) patients initially presented with a metastatic tumor, and all others had recurrences after initially localized disease. Sixty-seven percent of patients had 5 cancer types: non-small cell lung cancer (NSCLC) (10, 18%),[25,32,33,40-42,49,60,68,72] kidney (9, 16%),[24,45,58,64,66,75] melanoma (7, 13%),[28,38,48,54,65,70,71] lymphoma (6, 11%),[37,51,59,63,73] and hepatobiliary (5, 9.1%).[35,44,55-57]

Data pertinent to treatment characteristics are in Table 2. Treatment analysis was broken up into 3 phases: (1) prior treatment course, (2) treatment course leading up to an abscopal response, and (3) treatment during or after an abscopal response. All but 1 patient[75] received RT either at the time of an abscopal response or in prior courses of therapy. (1) Prior treatment courses were as follows (treatments in this phase were not mutually exclusive): 9 (16%) had RT,[28,33,38,41,46,53,63,72,74] 26 (47%) had surgery,[23,24,28,31,33,38-42,45,48,53-55,60,66-70,74-76] 23 (42%) had chemotherapy,[23,27,28,31,32,35,36,38,40-42,48,49,51,53,56,59,63,67,68,70-72] and 14 (25%) had immunotherapy.[28,29,32,39,41,45,53,54,65,67,68,70,72,76] (2) During the course of treatment leading up to an abscopal response, 34 (62%) patients received RT alone,[24,32-34,36,37,40,43-45,46,49,51-53,55,56,57-59,62,64,66-69,71,73,74,76] 5 (9.1%) underwent surgery with RT,[25,27,28,35,54] 4 (7.3%) received chemotherapy with RT,[28,39,45,61] and 11 (20%) received immunotherapy with RT.[29,31,38,41,42,54,60,65,68,70,72] (3) Treatments during or after the abscopal response were as follows: 22 (40%) patients received RT only to their primary tumor[27,29,31,35-37,39,42,43,45,46,49,52,57-59,68,71,73,76] and 29 (53%) received RT only to a metastasis.[23-25,28,32,33,38,40,41,43-45,48,51,53-56,60,64-67,69,70,72,74] Three (5.5%) patients received RT to both the primary tumor and a metastasis,[34,61,62] but still experienced the abscopal response at a distant site from radiation (Table 2). Only 1 (1.8%) patient did not receive RT during the course of treatment leading to an abscopal response, but had a history of prior RT (Table 2).[63] Targeted therapy was documented in 8 (15%) cases.[24,43,48,53,54,60,67,68] The median reported radiation dose and dose per fraction were 32 Gy (IQR, 25.5-48 Gy; min 12 Gy, max 73.6 Gy) and 3 Gy per fraction (IQR, 2-7.2 Gy per fraction; min 1.5 Gy per fraction, max 48 Gy per fraction).

Ninety-six percent of the articles selected in this work demonstrated a clear abscopal effect as defined by the result of any local therapy affecting a distant, untreated tumor (Table 2). The median time until an abscopal effect was 3 months (IQR, 1-5; min 0.5, max 24). Median follow-up time after the abscopal effect was 18.5 months.[23-27,28-56,58-67,69-72,74] New metastases occurred in 16 (29%) patients postabscopal effect,[24,31,32,38,45,49,51,54,60,64,66,67,69,71,72,74] whereas the rest of the 39 (71%) patients had stable disease during case follow-up Figure 3. depicts Kaplan-Meier curves showing a 5-year overall survival of 63% and a 5-year progression-free survival of 45%. Univariate analysis was performed to explore factors that correlate to patient survival and development of new metastases. No variables had statistical significance in predicting duration of response or survival (Table 3).

Discussion

This is the first patient-level data meta-analysis of reported abscopal effects. We found that 67%

Table 2 Included articles demonstrating abscopal effect

Study	Year	True defined*	Sex	Age	Cancer type	RT to primary	RT to metastasis	RT at multiple sites	RT total dose (Gy)	RT fx	Average RT dose/ fx (Gy)	BED	RT only	RT + surgery	RT + chemotherapy	RT + IT	Follow- up time (mo)	Outcome	New met
Cotter et al[74]	2011	Y	M	70	39	N	Y	N	12	2	6	19.2	Y	N	N	N	25	Alive	Y
Ebner et al[69]	2017	Y	M	75	13	N	Y	N	73.6	16	4.6	107	Y	N	N	N	46	Dead	Y
		Y	M	85	13	N	Y	N	50.4	12	4.2	71.5	Y	N	N	N	92	Alive	N
Fairlamb[66]	1981	Y	F	73	23	N	Y	N	40	15	2.7	50.6	Y	N	N	N	56	Alive	Y
Golden et al[72]	2013	Y	M	64	41	N	Y	N	30	5	6	48	N	N	N	Y	10	Alive	Y
Antoniades et al[73]	1977	Y	M	44	55	Y	N	N	30	20	1.5	34.5	Y	N	N	N	-	Alive	N
		Y	M	40	55	Y	N	N	30	20	1.5	34.5	Y	N	N	N	-	Alive	N
Cong et al[68]	2017	Y	F	64	41	Y	N	N	37.5	5	7.5	65.6	N	N	N	Y	-	Alive	N
Desar et al[67]	2016	Y	M	19	47	N	Y	N	30	10	3	39	Y	N	N	N	6	Dead	Y
Joe et al[61]	2017	Y	F	57	14	Y	Y	Y	54	30	1.8	63.7	N	N	Y	N	48	Alive	N
Lakshmanagowda et al[59]	2009	Y	F	65	55	Y	N	N	24	12	2	28.8	Y	N	N	N	6	Alive	N
MacManus et al[58]	1994	Y	M	58	23	Y	N	N	20	10	2	24	Y	N	N	N	9	Dead	N
Nam et al[44]	2005	Y	M	65	21	N	Y	N	30	-	-	-	Y	N	N	N	15	Alive	N
Ohba et al[56]	1998	Y	M	76	21	N	Y	N	36	-	-	-	Y	N	N	N	25	Alive	N
Okuma et al[55]	2011	Y	M	63	21	N	Y	N	60.8	27	2.2	74.4	Y	N	N	N	54	Alive	N
Postow et al[70]	2012	Y	F	33	25	N	Y	N	28.5	3	9.5	55.5	N	N	N	Y	10	Alive	N
Rees and Ross[52]	1983	Y	M	49	16	Y	N	N	40	20	2	48	Y	N	N	N	20	Dead	-
Robins et al[51]	1981	Y	F	59	55	N	Y	N	20	10	2	24	Y	N	N	N	4	Dead	Y
Stamell et al[71]	2012	Y	M	67	25	Y	N	N	24	3	8	43.2	Y	N	N	N	84	Alive	Y
Takaya et al[46]	2007	Y	F	69	10	Y	N	Y	22	10	2.2	26.8	Y	N	N	N	12	Alive	N
Wersäll et al[45]	2009	Y	F	83	23	Y	N	N	32	4	8	57.6	Y	N	N	N	-	Alive	N
		Y	F	64	23	N	Y	N	-	-	-	-	N	N	Y	N	54	Alive	N
		Y	M	69	23	N	Y	N	30	2	15	75	Y	N	N	N	24	Alive	Y
		Y	F	55	23	Y	N	N	32	4	8	57.6	Y	N	N	N	-	Alive	N
Sullivan et al[48]	2013	Y	M	68	25	N	Y	N	-	-	-	-	N	N	N	N	13	Alive	N
Hiniker et al[65]	2012	Y	-	-	25	N	Y	N	-	-	-	-	N	N	N	Y	-	Alive	N
Isobe et al[63]	2009	N	F	65	55	N	N	N	40	-	-	-	N	N	N	N	60	Alive	N
Joe et al[61]	2018	Y	M	74	16	Y	Y	Y	30	10	3	39	Y	N	N	N	14	Alive	N
Kodama et al[60]	2013	Y	M	74	41	N	Y	Y	48	24	2	57.6	N	N	N	Y	61	Dead	Y
Nakanishi et al[57]	2008	Y	M	79	21	Y	N	N	48	1	48	278	Y	N	N	N	-	Alive	N

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Table 2 (*Continued*)

Study	Year	True defined*	Sex	Age	Cancer type	RT to primary	RT to metastasis	RT at multiple sites	RT total dose (Gy)	RT fx	Average RT dose/ fx (Gy)	BED	RT only	RT + surgery	RT + chemotherapy	RT + IT	Follow- up time (mo)	Outcome	New met
Okwan-Duodu et al[54]	2015	Y	F	50	25	N	Y	N	-	-	-	-	N	Y	N	Y	20	Alive	Y
Hamilton et al[25]	2018	Y	M	47	41	N	Y	N	25	5	5	37.5	N	Y	N	N	7	Alive	N
Gutkin et al[38]	2018	Y	M	57	25	N	Y	N	54	3	18	151	N	N	N	Y	78	Alive	Y
Chino et al[40]	2018	Y	M	58	41	N	Y	N	60	8	7.5	105	Y	N	N	N	18	Alive	N
Leung et al[34]	2018	Y	F	65	7	Y	Y	Y	225	15	15	562	Y	N	N	N	60	Alive	N
Sperduto et al[28]	2017	Y	F	36	25	N	Y	Y	25	5	5	37.5	N	Y	Y	N	120	Alive	N
Van de Walle et al[24]	2016	Y	F	66	23	N	Y	N	39	13	3	50.7	Y	N	N	N	17	Alive	Y
Zhao et al[23]	2018	Y	M	65	16	N	Y	N	42	6	7	71.4	Y	N	N	N	15	Alive	N
Katayama et al[33]	2017	Y	M	63	41	N	Y	Y	45	15	3	58.5	Y	N	N	N	9	Alive	N
Britschgi et al[41]	2018	Y	M	47	41	N	Y	N	18	3	6	28.8	N	N	N	Y	24	Alive	N
Kim and Kim[35]	2019	Y	M	70	21	Y	N	N	48	4	12	105	N	Y	N	N	21	Alive	N
Bitran[42]	2019	Y	F	62	41	Y	N	N	27	9	3	35.1	N	N	N	Y	54	Alive	N
Shinde et al[29]	2019	Y	M	75	20	Y	N	Y	14.8	2	7.4	25.7	N	N	N	Y	10	Alive	N
Lin et al[32]	2019	Y	M	71	41	N	Y	N	48	8	6	76.8	Y	N	N	N	19	Alive	Y
Brenneman et al[36]	2019	Y	F	67	47	Y	N	N	50	25	2	60	Y	N	N	N	18	Alive	N
Sato et al[31]	2016	Y	M	54	18	Y	N	N	48	24	2	57.6	N	N	N	Y	5	Dead	Y
Shi et al[27]	2017	Y	F	67	43	Y	N	N	45	15	3	58.5	N	Y	N	N	1	Dead	N
Hidaka et al[37]	2017	Y	M	88	55	Y	N	Y	32	8	4	44.8	Y	N	N	N	6	Dead	N
Barsky et al[39]	2019	Y	M	67	24	Y	N	N	30	10	3	39	N	N	Y	N	7	Dead	N
Siva et al[49]	2013	Y	F	78	41	Y	N	Y	60	30	2	72	Y	N	N	N	2	Alive	Y
Ishiyama et al[64]	2012	Y	M	61	23	N	Y	Y	18	1	18	50.4	Y	N	N	N	34	Alive	Y
Poon and Wong[53]	2017	Y	M	79	45	N	Y	Y	24	4	6	38.4	Y	N	N	N	6	Alive	N
Azami et al[43]	2018	Y	F	64	7	Y	Y	Y	60	30	2	72	Y	N	N	N	21	Alive	N
Masue et al[75]	2007	N	M	58	23	N	N	N	-	-	-	-	N	N	N	N	46	Alive	N
Agyeman et al[76]	2019	Y	M	56	47	Y	N	N	40	20	2	48	Y	N	N	N	17	Alive	N

Abbreviations: BED = biologically effective dose, assuming an $\alpha:\beta$ ratio of 10; fx = fraction; IT = immunotherapy; met = metastasis; RT = radiation therapy.

* Refers to whether or not the article demonstrates a true abscopal response (as defined by the result of any local therapy affecting a distant, untreated tumor).

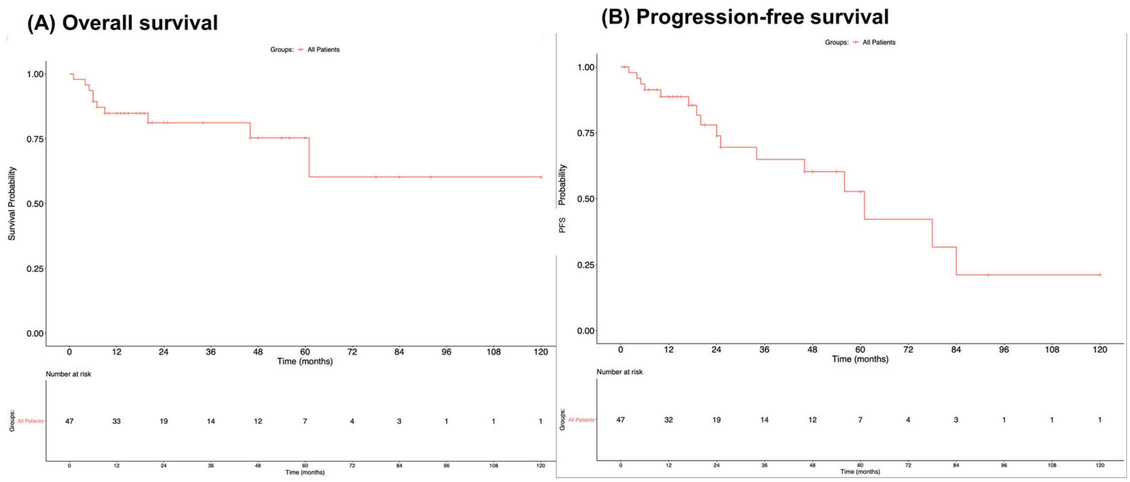

Figure 3 Kaplan-Meier curves. **(A)** Overall survival at 5 years was 63%. **(B)** Progression-free survival at 5 years was 45%.

of abscopal responses were reported in NSCLC, kidney cancer, melanoma, lymphomas, and hepatobiliary cancers. Five years after an abscopal response, 55% of patients had disease progression and 63% were alive, which suggested these patients with metastatic cancer had a relatively favorable and indolent biology. All reported cases of the abscopal response were after RT, but not other local treatments like surgery. There

Table 3 **Predictors of overall survival and progression-free survival after abscopal response**

	Univariate hazard ratio	95% CI	*P* value	Multivariate hazard ratio	95% CI	*P* value
Overall survival						
Surgery						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.9	0.12-7.60	.96	1.16	0.11-12.13	.9
Chemotherapy						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.63	0.08-5.01	.66	0.46	0.04-4.79	.51
Immunotherapy						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.68	0.14-3.22	.63	0.6	0.12-2.92	.52
BED 10 Gy increase	0.99	0.96-1.01	.29	0.99	0.96-1.01	.3
Progression-free survival						
Surgery						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.46	0.06-3.57	.46	3.7 × 10^-9	0-Inf	.99
Chemotherapy						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.32	0.04-2.42	.27	0.93	0.11-7.73	.95
Immunotherapy						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.97	0.70-5.59	.2	1.21	0.39-3.80	.74
BED 10 Gy increase	0.99	0.98-1.01	.42	0.99	0.98-1.01	.36

Abbreviations: BED = biologically effective dose; CI = confidence interval; Ref = reference value.

were no known predictors of duration of response or survival.

Preclinical data suggested surgery did not boost the abscopal response[77] nor did it induce antigen-specific immune responses in patients with prostate cancer, whereas radiation did.[78] Furthermore, preclinical data combining focal RT with anti-programmed cell death protein 1 (anti-PD1/PDL1) agents (PD-1 is an immune checkpoint) demonstrated abscopal responses more reliably with higher doses per fraction than without combination.[6] In clinical reports, patients with dramatic changes to their T-cell repertoire were more likely to be responders.[15] Although these effects were hypothesized, 25% of patients in this work received immunotherapy but did not appear to have improvement in progression-free survival or overall survival, compared with patients who did not receive immunotherapy. Additionally, there was no apparent effect of radiation dose, dose per fraction, or treatment location (primary vs metastasis vs both) on outcomes.

Several case reports and retrospective studies have shown relationships between RT and immunotherapy in certain cancer types.[16,17] Prospective trials in metastatic head and neck squamous cell carcinoma by McBride et al[79] found the combination of stereotactic body RT (SBRT) and checkpoint blockade did not improve objective response rate in nonirradiated lesions or overall survival in unselected patients with metastatic disease. Yet, this approach was moderately predictive for overall survival in patients based on human papilloma virus status and PD1 status. A study by Theelen et al[80] examined the effects of pembrolizumab in activating the tumor microenvironment in NSCLC. They discovered that administering SBRT before pembrolizumab doubled the overall response rate, but did not meet the prespecified endpoint, so larger studies are needed to fully examine this relationship.

Limitations of this analysis are as follows: first, recognizing a true abscopal effect as an example of clear systemic response may be obscured by bias in how the abscopal effect is reported. Distinguishing abscopal effects from spontaneous regression and the bystander effect can be highly subjective, and may cause underreporting or misreporting of abscopal responses by clinicians. There is heterogeneity for how an abscopal response is defined (regression at some untreated lesions vs regression at all untreated lesions). Second, the utilization of second or third line treatment, in addition to RT, may cause difficulty in deciphering the precise treatment that generated the abscopal effect. Finally, the study lacked a control group, so although the abscopal effect is extremely rare, it remains difficult to assess how these patients performed in comparison to patients of a similar cohort that did not exhibit an abscopal effect. In the primary literature, the magnitude of the abscopal response was often not documented. Not every case report of the abscopal effect is being published and not every study reported the same duration of follow-up in the same manner. To keep the data consistent, progression free survival and overall survival were used for gauging abscopal response.

To better study the abscopal effect in the future, there must be an emphasis on standardizing how the abscopal response is reported and monitoring for reporting bias within case reports. It has been reported that the peak PD1 upregulation can occur 4 to 6 days after tumor irradiation. Afterward, the expression of PD1 will decrease gradually.[11] More work remains to be done for how to place various immunologic, pharmacologic, and radiotherapeutic mechanisms on a definitive abscopal effect timeline. To completely assess abscopal effects, a full timeline of disease evolution must be determined, and potential confounders must be accounted for in addition to evaluating the type of RT administered (SBRT vs conventionally fractionated RT). Future research should also consider investigating biomarkers, clinical parameters, and other methods to guide studies into the abscopal effect.

Conclusion

This is the first patient-level data meta-analysis of reported abscopal effects. We found that 67% of abscopal responses were reported in NSCLC, kidney cancers, melanomas, lymphomas, and hepatobiliary cancers. Ninety-six percent of the articles selected in this work demonstrated a clear abscopal effect as defined by the result of any local therapy affecting a distant, untreated tumor. Five years after an abscopal response, 55% of patients had disease progression and 63% were alive. Almost every reported case of the abscopal effect was after RT, and only rarely in other local treatments like surgery. There were no known clinical predictors of duration of response or survival.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.100909.

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