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ORIGINAL REPORT

Efficacy of Skin-Directed Therapy for Cutaneous Metastases From Advanced Cancer: A Meta-Analysis

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ABSTRACT

Purpose
To perform the first meta-analysis of the efficacy of skin-directed therapies for cutaneous metastases.

Methods
MEDLINE, EMBASE, The Cochrane Library, and ClinicalTrials.gov databases were searched for reports of prospective clinical studies published between 1960 and 2013 that assessed the response of skin-directed therapy for cutaneous metastases (47 of 2,955 unique studies were selected). Primary end points of the study were complete and objective response rates. Secondary analyses were preplanned and included subgroup analyses by skin-directed therapy, histology, and recurrence rates. Meta-analyses were performed with random-effect modeling, and extent of heterogeneity between studies was determined with the Cochran Q and I^2 tests.

Results
After applying exclusion criteria, 47 prospective studies of 4,313 cutaneous metastases were assessed. Five skin-directed therapies were identified: electrochemotherapy, photodynamic therapy, radiotherapy, intralesional therapy, and topical therapy. Among all cutaneous metastases, complete response rate was 35.5% (95% CI, 27.6% to 44.3%) and objective response rate was 60.2% (95% CI, 50.6% to 69.0%). Overall recurrence rate was estimated to be 9.2% (95% CI, 3.7% to 21.2%). Melanoma and breast carcinoma comprised 96.8% of all cutaneous metastases studied and had similar objective response rates (54.5% [95% CI, 48.3% to 60.7%] and 54.0% [95% CI, 48.3% to 59.7%], respectively). Grade ≥ 3 toxicity was reported in less than 6% of patients.

Conclusion
Response to skin-directed therapy for cutaneous metastases is high but heterogeneous across treatment modalities, with low rates of recurrence post-treatment. Treatment was generally well tolerated and conferred improvements in quality of life. Standardization of response criteria for cutaneous metastases and treatment algorithms to optimally use the available skin-directed therapies are needed.

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INTRODUCTION

Although less common than primary skin cancers, cutaneous metastases (CMs) are not a rare manifestation of malignancy. A meta-analysis of 22,297 patients with solid tumors estimated that 5.3% developed CMs.[1] It is therefore estimated that in 2013, 77,166 of the 1,455,960 newly diagnosed cancers in the United States (excluding cancers of the integument or hematologic malignancies) will develop CMs.[2] This does not include 45% of patients with metastatic melanoma who also develop CMs.[3]

With advances in the treatment of metastatic cancer, patients are living longer and are more likely to experience the sequelae of advanced disease, such as CMs. CMs can cause considerable morbidity, serving as a nidus for infection, bleeding, disfigurement, or pain (Appendix Fig A1, online only).[4-6] Shimozuma et al[7] demonstrated that, among women with advanced or recurrent breast cancer, CMs were associated with the greatest negative effect on quality of life (QOL). Systemic therapy alone often has limited efficacy with CMs, but skin-directed therapy has the potential to yield improved disease response and symptom palliation.[8-14]

For readers unfamiliar with the various forms of skin-directed therapy discussed herein, a brief summary is provided. Electrochemotherapy (ECT) for CMs uses short electric pulses directed at the tumor to permeabilize cell membranes to increase

the absorption of either intralesional or intravenous chemotherapy. Photodynamic therapy (PDT) for CMs uses a nontoxic light to activate a topical or intravenous photosensitizer that interacts with tissue oxygen to generate toxic free radicals for its cytotoxic effects. Radiotherapy (RT) delivers ionizing radiation to the CMs and kills tumor cells by generating free hydroxyl radicals and causing direct DNA damage. Intralesional therapy (ILT) relies on the administration of an antineoplastic agent directly into or adjacent to the CM. Topical therapy (TT) is the application of an antineoplastic agent directly onto the CM.

The benefit of directed local therapy for other organ metastases, such as bone,[15,16] spine,[17] and brain metastases,[18] has been the focus of several large randomized trials and meta-analyses designed to optimize treatment and disease control and maximize QOL. However, a limited number of prospective studies have been conducted on the treatment of CMs across a multitude of skin-directed treatment modalities. Thus, we conducted a meta-analysis on treatment efficacy of skin-directed therapies for CMs.

METHODS

Study Selection

Systematic literature searches were conducted (September 10, 2013) in four databases (MEDLINE [via PubMed], EMBASE, The Cochrane Library, and ClinicalTrials.gov) for human-only studies written in English from January 1, 1960, through September 10, 2013. Controlled vocabulary was leveraged as well as text words in the development of the search strategies. All search results were combined in a bibliographic management tool, and duplicates were eliminated both electronically and manually.

The search strategy contained two major components linked together with the AND operator: (1) skin-directed therapy: surgery, excision, topical, intralesional therapy, injection, photodynamic, photochemotherapy, electrochemotherapy, radiation, radiotherapy, brachytherapy AND (2) skin metastasis: cutaneous metastasis/metastases, dermal metastasis/metastases.

After combining the two concepts, the results were limited (by using filters) to studies in English and those regarding humans only in PubMed and EMBASE. For databases that did not have a filter (The Cochrane Library and ClinicalTrials.gov) to eliminate undesired languages and animal studies, those were excluded during the investigator's assessment of the records. For a complete list of Medical Subject Headings and keyword terms used, refer to the PubMed search strategy in the Data Supplement.

Two investigators (D.E.S. and E.A.G.S.) independently reviewed all records from the initial search strategy by using a four-stage study-selection process. During stage 1, all 2,955 record titles and abstracts (if available) were reviewed to detect potentially relevant records (details of exclusion criteria and reason for exclusion are included in the Data Supplement). During stage 2, all full-length articles and meeting abstracts that passed stage 1 were reviewed to identify studies that had extractable response data for a skin-directed local therapy for CM (Data Supplement). The definition of a CM (*v* primary cutaneous malignancy) was determined by the reporting author and was assumed to be valid. Importantly, studies were excluded at this stage that grouped lymph node metastases with CMs. During stage 3, studies that re-reported data from the same trials were systematically removed, yielding 107 eligible studies. Finally, during stage 4, study design was assessed, and only prospective studies were eligible for analysis.

Data Extraction

D.E.S. and E.A.G.S. independently extracted data from the 47 studies. Data extracted (Appendix Tables A1-A8, online only) included patient and CM characteristics; treatment characteristics, including the use of concurrent systemic therapy and skin-directed treatment details; response rates and criteria used for complete response (CR), partial response (PR), stable disease, progressive disease, objective response rates (ORRs) and overall recurrence rates; toxicity and QOL findings and scales used; and level of evidence and data quality.

End Point Definitions

Primary end points of the study were CR and ORR of all studies. CR was chosen rather than PR, stable disease, or progressive disease because it was deemed the least subjective assessment of response (Table 1). CR and ORRs were study defined; if not explicitly stated, ORR equaled CR plus PR. Secondary analyses were preplanned and included response rates by skin-directed treatment modality, histology, and recurrence rates. Histology subgroup analyses were performed after the study had been divided by histology when feasible. A recurrence was defined as a CM that initially underwent an objective response and subsequently recurred within the treatment field. Toxicity and QOL data were analyzed qualitatively secondary to the multiple toxicity scales used and lack of consistent reporting of specific toxicities to enable pooled analyses. In studies without formal toxicity grading scales, the words "serious" or "severe" were interpreted as grade 3 toxicities, and "life-threatening" was interpreted as grade 4 toxicity.

Assessment of Data Quality and Reporting Risk of Bias

Level of evidence was collected by using standard definitions from the National Cancer Institute (Appendix Table A8).[64] Randomized controlled trials (RCTs) were assessed by the Jadad scale (Appendix Table A7).[65] Formal statistical analyses for publication bias were performed with funnel plots and Egger's test.

Statistical Analysis

For all analyses of CR, ORRs, and recurrence rates, odds ratios were calculated with 95% CIs. For meta-analysis, both a fixed-effects model and a random-effects model were considered. However, extent of heterogeneity was significant; thus, a random-effects model was reported for all analyses. Extent of heterogeneity between studies was performed with the Cochran *Q* test, and an I^2 test. All probability values were two-tailed with $P = .05$. Toxicity calculations were reported as crude rates. To estimate the adjusted event rate when correcting for publication bias, the Duval and Tweedie trim-and-fill method was used.[66] Statistical analyses were performed by using Comprehensive Meta-Analysis, version 2, software (Biostat, Englewood, NJ).

RESULTS

Patient and Study Characteristics

Forty-seven studies reporting on 915 patients with 4,313 CMs were included for analysis. The median age in those studies was 61 years (range, 42 to 83 years); 306 patients were males (33.4%), 565 were females (61.7%); sex could not be extracted for 44 patients (4.8%). Histologies for the CMs were 582 (13.5%) breast cancer, 3,591 (83.3%) metastatic melanoma, nine (0.2%) unspecified sarcoma, four (0.09%) Kaposi's sarcoma, three (0.07%) mucosal squamous carcinoma of the head and neck, two (0.05%) angiosarcoma, two (0.05%) unknown primary, and 120 (2.8%) other or unspecified. Of the 47 prospective studies, eight were RCTs, 38 were nonrandomized trials, and one was a prospective case series of consecutive patients (Fig 1).

Primary End Points

Of the 4,313 CMs, 836 (19.4%) reported ORRs but not CRs and were excluded from CR meta-analyses. Across treatment modalities, 1,890 (54.4%) of the 3,477 assessable patients with CMs had a CR. Formal criteria for defining CRs were found in eight studies (17.0%) that used WHO criteria, five (10.6%) that used criteria similar to WHO, seven (14.9%) that used RECIST, and 24 (51%) that used a variety of definitions to suggest complete clinical and/or histologic

Table 1. Prospective Studies of Skin-Directed Therapies for Skin Metastases

Study	Year	No. of Patients	No. of Lesions	Local Therapy	No. of Lesions With CR	Definition of CR	No. of Lesions With Objective Response	Definition of Objective Response
Heller et al[44*]	1996	4	12	ECT	5	"Absence of any trace of tumor"	7	CR + PR
Sersa et al[11]	2000	9	27	ECT†	3	WHO, 1979	13	CR + PR
Rodriguez-Cuevas et al[45*]	2001	6	29	ECT	11	"Complete response"	27	CR + PR
Byrne et al[28]	2005	16	53	ECT	34	"No residual disease"	39	CR + PR
Gaudy et al[29]	2006	12	24	ECT†	11	"Total disappearance of the lesion"	14	CR + PR
Marty et al[23]	2006	41	171	ECT	126	WHO, 1997	145	CR + PR
Quaglino et al[46]	2008	14	233	ECT	136	WHO, 1997	216	CR + PR
Matthiessen et al[30]	2011	24	94	ECT	58	RECIST, 2000	76	CR + PR
Benevento et al[47]	2012	12	142	ECT	107	RECIST, 2000	131	CR + PR‡
Campana et al[21]	2012	35	35	ECT	19	RECIST, 2000	32	CR + PR
Kendler et al[22*]	2013	3	79	ECT	7	RECIST, 2009	7	CR + PR‡
Sperduto et al[48]	1991	20	20	PDT	4	"Clinical and pathologic regression of all tumor in the treatment field"	13	CR + PR‡
Cairnduff et al[49]	1994	5	14	PDT	5	"Absence of clinically evident tumor"	5	CR + PR‡
Baas et al[50]	1996	4	20	PDT†	15	"Complete response"	18	CR + PR‡
Kaplan et al[51]	1998	3	13	PDT	13	"Complete reduction of tumor"	13	CR + PR‡
Mang et al[52]	1998	8	86	PDT	79	"Complete response"	86	CR + PR‡
Overgaard et al[36]	1985	NA	15	RT	10	"Complete disappearance of the tumor in the irradiated field"	15	CR + PR
Menéndez et al[35]	2009	7	88	RT	52	"Complete response"	61	CR + PR
Cohen et al[53]	1978	18	766	ILT	NA	NA	647	Clinical and pathologic "regression"
Nathanson et al[54]	1979	22	22	ILT	3	"Complete disappearance"	10	CR + PR
Cascinelli et al[37]	1993	16	47	ILT	NA	NA	24	≥ 30% reduction in tumor volume
Stewart et al[55*]	1999	23	23	ILT	NA	NA	7	"Local regression"
Hoeller et al[56]	2001	7	7	ILT	2	"100% decrease size change of injected lesion"	5	CR + PR‡
Stopeck et al[57]	2001	29	29	ILT	1	"Disappearance of all of the clinical evidence of tumor"	5	≥ 25% reduction in product of perpendicular diameter
Radny et al[58]	2003	23	237	ILT	209	"Disappearance of all clinical evidence of the … tumor"	230	CR + PR‡
Oratz et al[59]	2003	25	244	ILT	114	100% tumor volume regression; response must last ≥ 28 days	130	CR + PR; Response must last ≥ 28 days
Byrne et al[28]	2005	16	19	ILT	5	"No residual disease"	6	CR + PR
Triozzi et al[60]	2005	NA	14	ILT	0	"Disappearance of all the clinical evidence of tumor"	0	CR + PR‡
Gonzalez et al[61]	2006	77	77	ILT	2	WHO§	7	CR + PR
Kimata et al[62]	2006	6	5	ILT	0	"Necrosis or disappearance of all tumor cells"	4	CR + PR‡
Gaudy et al[29]	2006	12	16	ILT†	2	"Total disappearance of the lesion"	6	CR + PR
Dummer et al[63]	2008	25	25	ILT†	3	"Absence of detectable residual disease maintained for a minimum of 4 weeks"	6	CR + PR
Hofmann et al[19]	2008	5	5	ILT	1	"Complete response" and "complete regression"	2	> 25% response to tumor volume; 1 CR + 1 SD‡

(continued on following page)

Table 1. Prospective Studies of Skin-Directed Therapies for Skin Metastases (continued)

Study	Year	No. of Patients	No. of Lesions	Local Therapy	No. of Lesions With CR	Definition of CR	No. of Lesions With Objective Response	Definition of Objective Response
Thompson et al[20]	2008	11	26	ILT	9	RECIST, 2000	11	CR + PR
Bedikian et al[25]	2010	85	255	ILT	4	RECIST, 2000	15	CR + PR
Weide et al[26]	2010	48	894	ILT	704	Disappearance of lesion; no regrowth for 6 months	710	CR + PR‡
Unger et al[27]	1992	24	24	TT	4	"Complete remission"	7	CR + PR‡
Unger et al[31]	1993	52	52	TT†	1	WHO§	11	CR + PR
Terwogt et al[32]	1999	30	30	TT	7	Complete disappearance of all treated lesions for ≥ 4 weeks	13	CR + PR
Smorenburg et al[33]	2000	18	18	TT†	0	WHO§	4	CR + PR‡
Leonard et al[24]	2001	24	19	TT†	2	WHO, 1979	8	CR + PR
Eilender et al[34*]	2006	42	24	TT†	1	Complete disappearance of all treated lesions for ≥ 4 weeks	7	CR + PR‡
Salazar et al[40]	2011	10	10	TT†	3	"Modified WHO criteria"§	7	CR + PR‡
Florin et al[41]	2012	5	45	TT	19	"Complete response"	44	CR + PR
Adams et al[42]	2012	10	10	TT†	0	"Absence of any detectable residual disease"	2	CR + PR
Plesnicar et al[43]	1982	19	19	ILT + RT	14	"Cleared completely"	15	CR + PR
Lai et al[12]	2003	7	7	TT + RT	3	Disappearance of all treated skin lesions ≥ 4 weeks	6	CR + PR
Green et al[38]	2007	10	178	TT + ILT	74	"Impalpable" and "disappear"	92	CR + PR
Li et al[39]	2010	11	11	TT + PDT	8	RECIST§	11	CR + PR

Abbreviations: CR, complete response; ECT, electrochemotherapy; ILT, intralesional therapy; NA, not available; PDT, photodynamic therapy; PR, partial response; RT, radiotherapy; SD, stable disease; TT, topical therapy.

*Study divided by histology for subgroup analyses (see Appendix Table A1, online only, for information on histology details by study).

†Concurrent systemic therapy used/allowed.

‡Definition not explicitly listed. Authors' definition used.

§Year of response criteria used not stated.

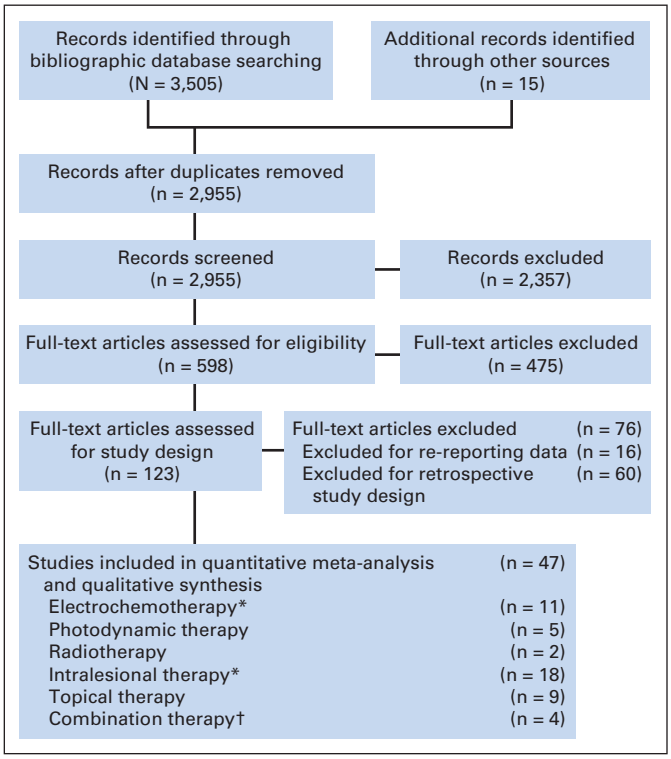

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature review process for skin-directed therapy of cutaneous metastases. (*) A randomized controlled trial comparing electrochemotherapy with intralesional therapy was divided by treatment modality. (†) More than one skin-directed therapy was used.

regression (Table 1). The CR rate for all included studies was 35.5% (95% CI, 27.6% to 44.2%) according to the random effects model (heterogeneity test, $Q = 661.907$; $I^2 = 93.201$; $P < .001$; Fig 2).

ORR

All 4,313 CMs were assessable for ORR analyses, of which 2,970 (68.9%) had ORRs. ORR was defined in 42 studies as the sum of CR plus PR, three used ≥ 25% reduction from pretreatment size, and two used other definitions (Table 1). The ORR for all studies was 60.2% (95% CI, 50.6% to 69.0%; $Q = 892.278$; $I^2 = 94.621$; $P < .001$; Fig 3).

Secondary End Points

For response by treatment modality, CR ranged from 12.9% (95% CI, 5.4% to 27.5%) for TT to 67.8% (95% CI, 38.8% to 87.4%) for PDT (Fig 4). By treatment modality, ORR ranged from 42.1% (95% CI, 22.3% to 64.9%) for TT to 83.8% (95% CI, 37.9% to 97.8%) for RT (Fig 5). Three of the four combination studies used TT, with CR rate of 58.0% (95% CI, 27.7% to 83.3%) and ORR of 78.1% (95% CI, 44.1% to 94.1%).

Histology

Breast carcinoma and melanoma represented 96.8% of the CMs analyzed. They had nearly identical ORRs of 54.5% (95% CI, 48.3% to 60.7%) and 54.0% (95% CI, 48.3% to 59.7%), respectively. Of the remaining histologies, responses ranged from 50% for Kaposi's sarcoma and angiosarcoma to 83% for adenocarcinoma of unknown primary and mucosal squamous carcinoma of the head and neck (Appendix Fig A2, online only).

Recurrence Rates

Eleven studies had extractable recurrence information for CMs after initial ORR. From the 4,313 CMs initially evaluable, 2,970 had an ORR, of which only 333 (11.2%) had recurrence information for analysis. Seventy-two lesions experienced a recurrence at time of last follow-up, with an overall recurrence rate estimated at 9.2% (95% CI, 3.7% to 21.2%; Appendix Fig A3, online only).

Qualitative Analyses

Twenty-three studies (48.9%) used a formal toxicity scale (15 used various forms of the Common Terminology Criteria for Adverse Events, seven used WHO, and one used a custom scale); an additional three studies reported toxicity grade but did not define the scale used (Appendix Table A5). Treatment was well tolerated in an estimated 862 (94.2%) of 915 patients (grade ≤ 2 toxicity or the equivalent). Thirty-nine patients (4.3%) experienced grade 3 local or systemic toxicity. Fourteen patients (1.5%) experienced grade 4 toxicities, three related to disseminated intravascular coagulation of unknown relation to the local ILT and seven related to various cytopenias or pleural effusion in a study that used concurrent systemic therapy with local ILT. The remaining four grade 4 toxicities were defined by exfoliative or ulcerative dermatitis.

Treatment site pain was highly treatment specific. In patients treated with ILT, pain was most commonly reported as injection site pain, which occurred in approximately 21% to 72% of patients and was often transient. Pain resolution after ECT varied across studies from near complete resolution to 49% of patients having mild pain 1 month post-treatment.[21,22] Local pain from PDT was reported to occur in up to 95% of patients and typically resolved within 3 weeks. Multiple TT studies reported local pain but did not report duration or resolution of pain symptoms. The two RT studies did not report on pain symptoms.

QOL

Five studies used formal measures to assess QOL: three used the visual analog scale, one used a custom four-point pain scale, and one used the Rotterdam Symptom Checklist and a Body Image Scale (Appendix Table A6).[12,21-24] QOL results demonstrated that treatment of CMs decreased psychological distress from baseline to last follow-up.[24] ECT increased mean pain scores up to 15 minutes post-treatment and reduced pain scores below pretreatment values thereafter.[22] Combined TT and RT reduced the number of daily wound dressing changes and pain scores.[12]

Publication Bias

A funnel plot of studies used to calculate CR rates (Appendix Fig A4, online only) demonstrated asymmetry that was confirmed with Egger's regression test ($P < .001$), indicating the presence of publication bias. When adjusting for this bias by using the trim-and-fill method, the original observed CR rate of 35.5% increased to 61.7% (95% CI, 52.6% to 70.1%). ORRs did not appear to be subject to significant publication bias, with relative symmetry present in the funnel plot (Appendix Fig A5, online only), confirmed with Egger's regression test ($P = .06$).

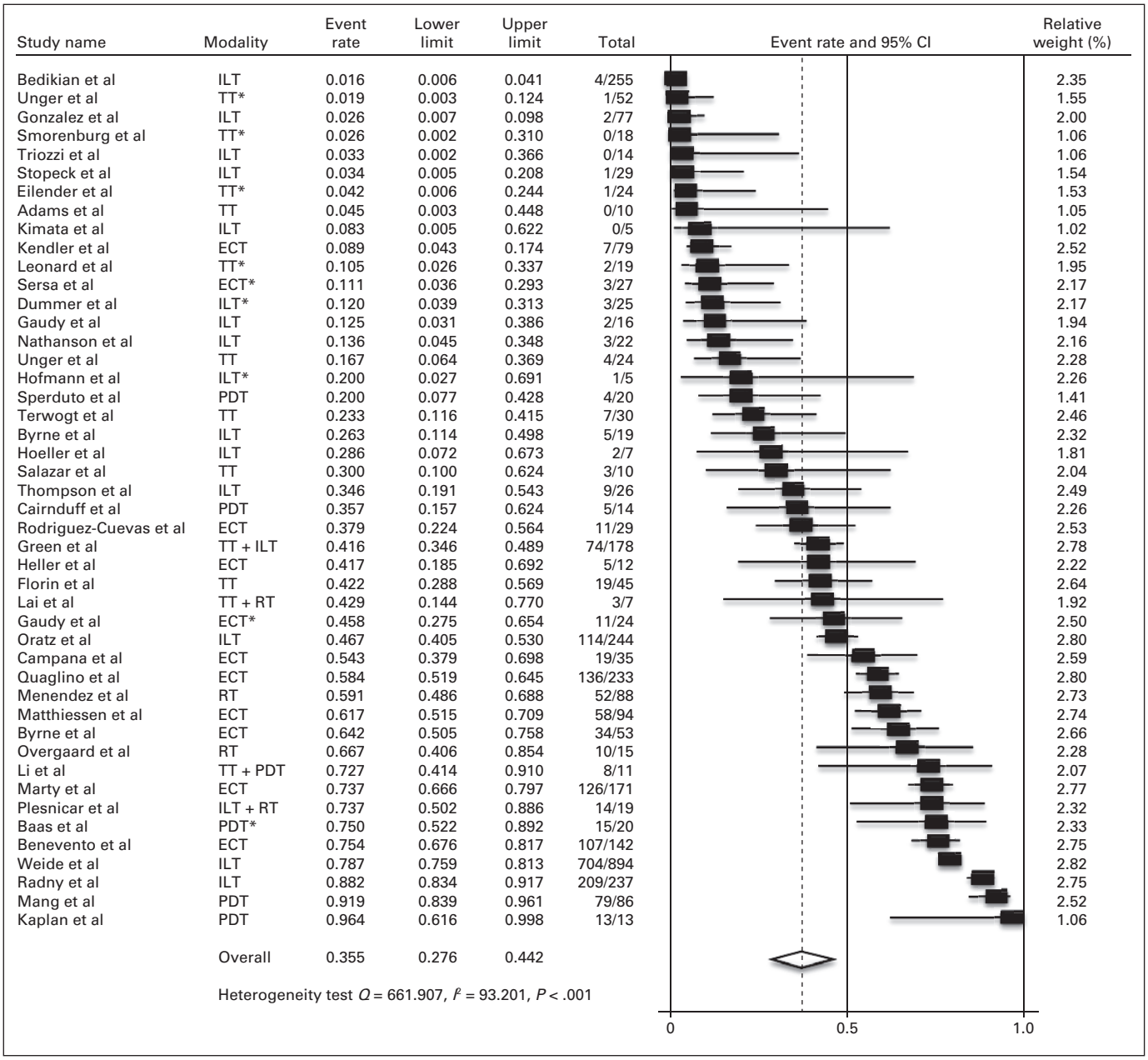

Fig 2. Meta-analysis of complete response. NOTE. Total column indicates No. of complete responses/No. of cutaneous metastases. ECT, electrochemotherapy; ILT, intralesional therapy; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy. (*) Concurrent systemic therapy was used and/or allowed.

DISCUSSION

Decreasing symptom burden through palliative treatment can improve QOL, a goal often secondary only to improving survival in patients with cancer.[67,68] CMs are increasingly prevalent and occur in approximately 10% of patients with metastatic cancer.[3] Some cancers have a predilection for CMs, such as breast carcinoma and melanoma, in which the rate of CMs is nearly the same as that for brain metastasis (25% and 45%, respectively).[1] Despite the prevalence of CMs, there are no guidelines for managing CMs with skin-directed therapy, and most textbooks reviewing CMs have little information on treatment.[69]

This meta-analysis was designed to ascertain the efficacy of a variety of skin-directed therapies commonly used to treat CMs. The data suggest that a majority of patients will respond to skin-directed therapy, and recurrence is infrequent. Moreover, toxicity appears minimal, and data suggest an improvement in QOL.[10,21,24] Systemic therapy alone often has limited efficacy in CMs, with several series reporting ORRs of approximately 25%.[8,11] The summary 60.2% ORR observed in this study clearly demonstrates the value of treating CMs with skin-directed therapy.

ECT typically involves electroporation of the cytotoxic drugs bleomycin and cisplatin. ECT has been shown to be more efficacious than ILT alone or systemic therapy alone.[28,29] A meta-analysis of ECT for cutaneous and/or subcutaneous malignancy (including primary nonmetastatic disease) reported a crude CR rate of 59%.[9] This is comparable with our crude CR rate of ECT for CMs of 57.5% (and the

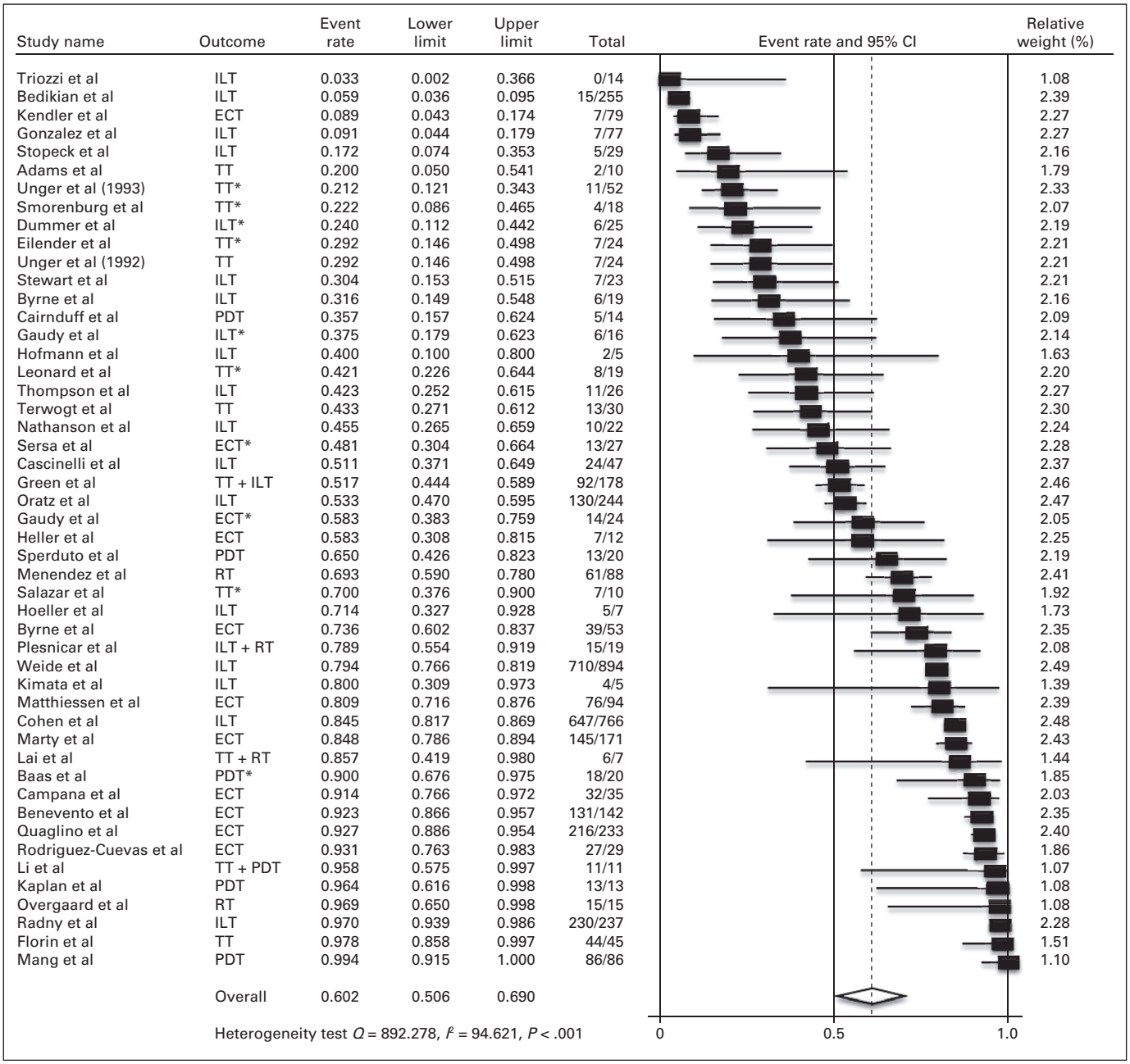

Fig 3. Meta-analysis of objective response. NOTE. Total column indicates No. of objective responses/No. of cutaneous metastases. ECT, electrotherapy; ILT, intralesional therapy; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy. (*) Concurrent systemic therapy was used and/or allowed.

estimated summary CR rate of 47.5%; Fig 3). ECT is often performed as an inpatient procedure and most commonly requires general anesthesia; however, studies have successfully used local anesthesia alone.[22] ECT is often performed in ≤ 30 minutes, but multiple treatments may be necessary. Pain is commonly reported, but general anesthesia can obviate this, and more than 90% of patients would agree to undergo another treatment if indicated.[23,30] ECT use, especially in Europe, appears to be increasing since the publication of the European Standard Operating Procedures for Electrochemotherapy in 2006, a multicenter study standardizing the use of ECT for both primary and metastatic cancers.[23,70,71]

PDT has been extensively studied for premalignant and primary skin cancers, with more than 40 RCTs analyzed in a systematic review in 2010.[72] However, there have been no RCTs of PDT for the treatment of CMs to date. Treatment times depend on whether an intravenous or topical photosensitizer is used but typically last less than 90 minutes. PDT is associated with treatment site pain that is mitigated by local anesthesia or oral analgesics.

RT is commonly used for the palliation of bone and brain metastases,[17,18,73] but only two prospective trials have assessed RT for treating CMs.[35,36] A unique advantage of RT is the ability to penetrate to any depth by selecting an appropriate type and energy of radiation.

Study name	Treatment Modality	Event rate	Lower limit	Upper limit	Relative weight (%)
Kendler et al	ECT	0.089	0.043	0.174	8.93
Sersa et al	ECT	0.111	0.036	0.293	7.84
Rodriguez-Cuevas et al	ECT	0.379	0.224	0.564	8.99
Heller et al	ECT	0.417	0.185	0.692	7.99
Gaudy et al	ECT	0.458	0.275	0.654	8.87
Campana et al	ECT	0.543	0.379	0.698	9.18
Quaglino et al	ECT	0.584	0.519	0.645	9.81
Matthiessen et al	ECT	0.617	0.515	0.709	9.62
Byrne et al	ECT	0.642	0.505	0.758	9.38
Marty et al	ECT	0.737	0.666	0.797	9.72
Benevento et al	ECT	0.754	0.676	0.817	9.67
	Overall	0.475	0.303	0.653	
	$Q = 100.79$, $I^2 = 90.09$, $P < .001$				
Bedikian et al	ILT	0.016	0.006	0.041	7.62
Gonzalez et al	ILT	0.026	0.007	0.098	6.59
Triozzi et al	ILT	0.033	0.002	0.366	3.64
Stopeck et al	ILT	0.034	0.005	0.208	5.18
Kimata et al	ILT	0.083	0.005	0.622	3.53
Dummer et al	ILT	0.120	0.039	0.313	7.09
Gaudy et al	ILT	0.125	0.031	0.386	6.40
Nathanson et al	ILT	0.136	0.045	0.348	7.06
Hofmann et al	ILT	0.200	0.027	0.691	4.76
Byrne et al	ILT	0.263	0.114	0.498	7.54
Hoeller et al	ILT	0.286	0.072	0.673	6.01
Thompson et al	ILT	0.346	0.191	0.543	8.02
Oratz et al	ILT	0.467	0.405	0.530	8.89
Weide et al	ILT	0.787	0.759	0.813	8.95
Radny et al	ILT	0.882	0.834	0.917	8.74
	Overall	0.214	0.120	0.354	
	$Q = 373.62$, $I^2 = 96.25$, $P < .001$				
Sperduto et al	PDT	0.200	0.077	0.428	21.63
Cairnduff et al	PDT	0.357	0.157	0.624	21.65
Baas et al	PDT	0.750	0.522	0.892	22.22
Mang et al	PDT	0.919	0.839	0.961	23.80
Kaplan et al	PDT	0.964	0.616	0.998	10.69
	Overall	0.678	0.389	0.875	
	$Q = 41.67$, $I^2 = 90.40$, $P < .001$				
Menendez et al	RT	0.591	0.486	0.688	54.00
Overgaard et al	RT	0.667	0.406	0.854	46.00
	Overall	0.627	0.228	0.905	
	$Q = 0.305$, $I^2 < 0.001$, $P = .581$				
Unger et al, 1993	TT	0.019	0.003	0.124	9.55
Smorenburg et al	TT	0.026	0.002	0.310	6.70
Eilender et al	TT	0.042	0.006	0.244	9.46
Adams et al	TT	0.045	0.003	0.448	6.62
Leonard et al	TT	0.105	0.026	0.337	11.79
Unger et al, 1992	TT	0.167	0.064	0.369	13.57
Terwogt et al	TT	0.233	0.116	0.415	14.54
Salazar et al	TT	0.300	0.100	0.624	12.30
Florin et al	TT	0.422	0.288	0.569	15.46
	Overall	0.129	0.054	0.275	
	$Q = 26.36$, $I^2 = 69.65$, $P = .001$				
Green et al	TT + ILT	0.416	0.346	0.489	29.96
Lai et al	TT + RT	0.429	0.144	0.770	21.53
Li et al	TT + PDT	0.727	0.414	0.910	22.98
Plesnicar et al	ILT + RT	0.737	0.502	0.886	25.53
	Overall	0.580	0.277	0.833	
	$Q = 9.46$, $I^2 = 68.29$, $P = .024$				

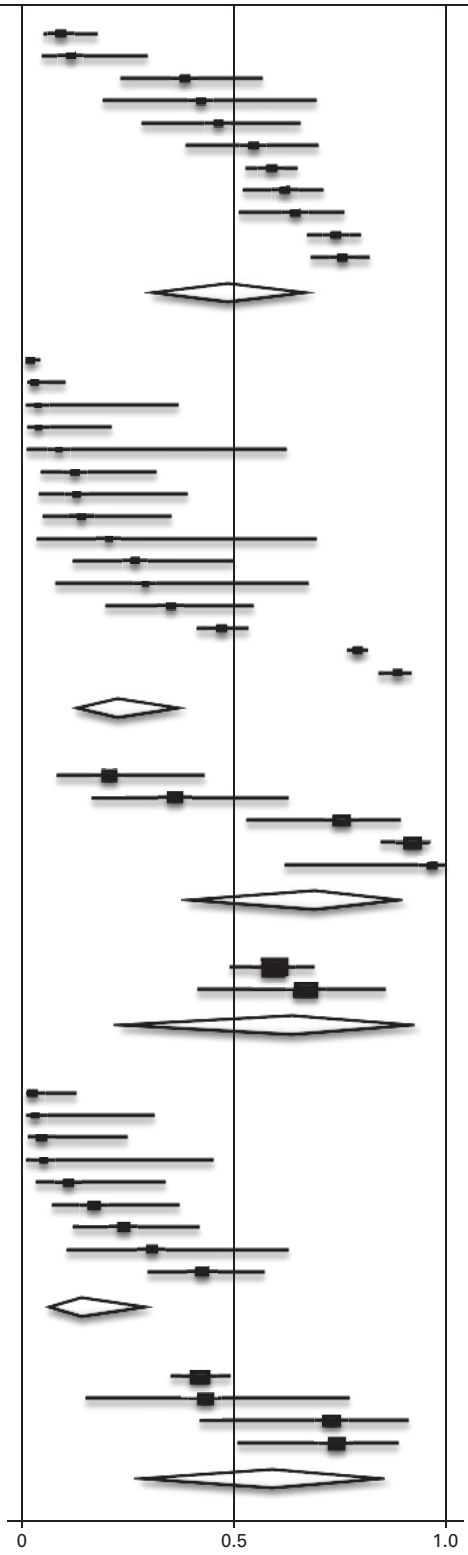

Fig 4. Meta-analysis of complete response by skin-directed therapy. ECT, electrochemotherapy; ILT, intralesional therapy; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy.

Study name	Treatment Modality	Event rate	Lower limit	Upper limit	Relative weight (%)
Kendler et al	ECT	0.089	0.043	0.174	9.20
Sersa et al	ECT	0.481	0.304	0.664	9.24
Heller et al	ECT	0.583	0.308	0.815	8.36
Gaudy et al	ECT	0.583	0.383	0.759	9.13
Byrne et al	ECT	0.736	0.602	0.837	9.51
Matthiessen et al	ECT	0.809	0.716	0.876	9.66
Marty et al	ECT	0.848	0.786	0.894	9.79
Campana et al	ECT	0.914	0.766	0.972	8.27
Benevento et al	ECT	0.923	0.866	0.957	9.50
Quaglino et al	ECT	0.927	0.886	0.954	9.69
Rodriguez-Cuevas et al	ECT	0.931	0.762	0.983	7.63
	Overall	0.754	0.577	0.873	
	$Q = 154.35$, $I^2 = 93.52$, $P < .001$				
Triozzi et al	ILT	0.033	0.002	0.366	2.94
Bedikian et al	ILT	0.059	0.036	0.095	6.26
Gonzalez et al	ILT	0.091	0.044	0.179	5.97
Stopeck et al	ILT	0.172	0.074	0.353	5.71
Dummer et al	ILT	0.240	0.112	0.442	5.77
Stewart et al	ILT	0.304	0.153	0.515	5.81
Byrne et al	ILT	0.316	0.149	0.548	5.70
Gaudy et al	ILT	0.375	0.179	0.623	5.63
Hofmann et al	ILT	0.400	0.100	0.800	4.37
Thompson et al	ILT	0.423	0.252	0.615	5.96
Nathanson et al	ILT	0.455	0.265	0.659	5.88
Cascinelli et al	ILT	0.511	0.371	0.649	6.21
Oratz et al	ILT	0.533	0.470	0.595	6.46
Hoeller et al	ILT	0.714	0.327	0.928	4.61
Weide et al	ILT	0.794	0.766	0.819	6.49
Kimata et al	ILT	0.800	0.309	0.973	3.75
Cohen et al	ILT	0.845	0.817	0.869	6.48
Radny et al	ILT	0.970	0.939	0.986	6.00
	Overall	0.445	0.295	0.606	
	$Q = 542.00$, $I^2 = 96.86$, $P < .001$				
Cairnduff et al	PDT	0.357	0.157	0.624	24.92
Sperduto et al	PDT	0.650	0.426	0.823	26.11
Baas et al	PDT	0.900	0.676	0.975	22.21
Kaplan et al	PDT	0.964	0.616	0.998	13.26
Mang et al	PDT	0.994	0.915	1.000	13.49
	Overall	0.837	0.562	0.954	
	$Q = 22.24$, $I^2 = 82.02$, $P < .001$				
Menendez et al	RT	0.693	0.590	0.780	68.26
Overgaard et al	RT	0.969	0.650	0.998	31.74
	Overall	0.838	0.379	0.978	
	$Q = 3.24$, $I^2 = 69.12$, $P = .072$				
Adams et al	TT	0.200	0.050	0.541	9.73
Unger et al, 1993	TT	0.212	0.121	0.343	12.46
Smorenburg et al	TT	0.222	0.086	0.465	11.19
Unger et al, 1992	TT	0.292	0.146	0.498	11.90
Eilender et al	TT	0.292	0.146	0.498	11.90
Leonard et al	TT	0.421	0.226	0.644	11.81
Terwogt et al	TT	0.433	0.271	0.612	12.32
Salazar et al	TT	0.700	0.376	0.900	10.39
Florin et al	TT	0.978	0.858	0.997	8.30
	Overall	0.421	0.223	0.648	
	$Q = 31.90$, $I^2 = 74.92$, $P < .001$				
Green et al	TT + ILT	0.517	0.444	0.589	34.39
Plesnicar et al	ILT + RT	0.789	0.554	0.919	29.36
Lai et al	TT + RT	0.857	0.419	0.980	20.64
Li et al	TT + PDT	0.958	0.575	0.997	15.62
	Overall	0.781	0.441	0.941	
	$Q = 11.05$, $I^2 = 72.86$, $P = .011$				

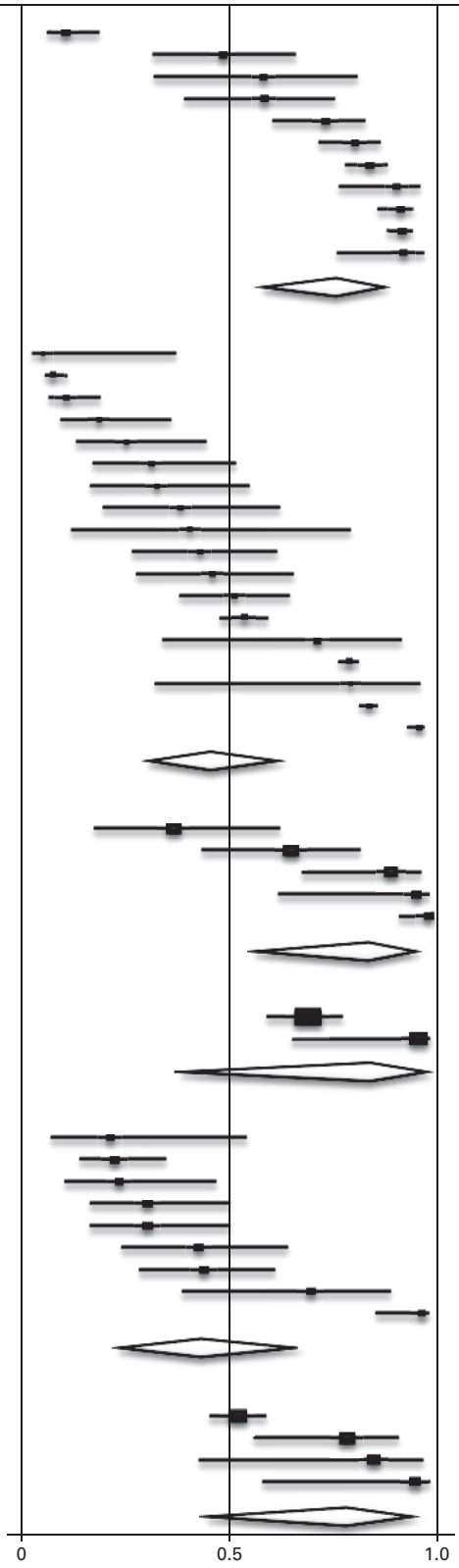

Fig 5. Meta-analysis of objective response by skin-directed therapy. ECT, electrochemotherapy; ILT, intralesional therapy; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy.

Treatments are typically given in several fractions over a period of weeks. Two studies used RT as part of combination therapy; high ORRs were observed, demonstrating the ability of TT or ILT to interact favorably with RT. Adverse effects primarily consist of local inflammatory symptoms.

ILT typically involves the injection of cytotoxic or immunomodulatory agents directly or perilesionally to the CMs.[28,37] Despite two RCTs demonstrating superior efficacy of ECT over ILT, ILT can be a simple and effective treatment with limited adverse effects. ECT often requires general anesthesia, but ILT requires only local anesthesia. ILT often requires multiple treatment visits, with the majority of studies reporting two or more visits, and some reporting five or more visits.

TT for CMs was originally described using miltefosine, but three prospective trials with imiquimod have recently been reported. Both agents rely on enhancing the immune response against tumor cells. Most studies reported a median duration of therapy of $\geq$ 8 weeks, with some more than 1 year. Topical monotherapy appeared to have the lowest response rates in this meta-analysis; however, response rates were improved in the three studies that combined TT with another skin-directed therapy.[12,38,39]

We detected a less common form of publication bias among the studies analyzed; CR rates were significantly greater in larger studies. The reason for this is unclear but could be a result of factors associated with the ability to conduct a large study. Experienced institutions with a large volume of CMs were likely able to conduct larger studies and may have selected patients for successful treatment more effectively. These institutions may have also had more technical sophistication which led to improved outcomes. A related possibility is that treatment efficacy improved over time. To explore this possibility, an analysis was performed to determine whether year of publication was associated with response rates. There was no correlation between CR or ORR and year of publication (data not shown).

The analyses presented here had some limitations. Our study demonstrated significant study heterogeneity; hence, a conservative estimate of response by using a random-effects model was performed. Although all studies but one were prospective clinical trials, only 17% were RCTs. There is likely inherent bias in patient selection for particular skin-directed therapies (many of which have been shown to affect skin-directed therapy outcome), such as tumor size,[74] number of CMs,[21] and depth of invasion,[41] which we were unable to standardize and integrate into our analyses. Because of these limitations, direct comparison of outcomes by treatment modality was not performed. Studies were limited to those in the English language, which may have introduced bias. Prospective data on surgical excision of CMs exclusively was not found in our literature search (metastasectomy trials often grouped resection of lymph nodes and CM resection together).[75,76] Finally, response criteria were heterogeneous. However, we extensively recorded and categorized the response criteria to aid in the interpretation of the data.

In conclusion, this study was designed to elucidate the efficacy of skin-directed therapies for CMs. The results suggest that response rates were heterogeneous but high, with low recurrence rates and minimal toxicity. In addition, improvements in QOL were reported. To develop evidence-based guidelines and improve outcomes for the treatment of CM, response, criteria will need to be standardized, and RCTs will be necessary to define treatment algorithms on the basis of specific patient and CM characteristics, and an improved grasp of the potential benefits of combination or sequential skin-directed therapies is requisite. Skin-directed therapy should be considered an effective component of the cancer treatment armamentarium.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Final approval of manuscript: All authors

REFERENCES

1. Krathen RA, Orengo IF, Rosen T: Cutaneous metastasis: A meta-analysis of data. South Med J 96:164-167, 2003
2. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. CA Cancer J Clin 63:11-30, 2013
3. Lookingbill DP, Spangler N, Helm KF: Cutaneous metastases in patients with metastatic carcinoma: A retrospective study of 4020 patients. J Am Acad Dermatol 29:228-236, 1993
4. Gehl J, Geertsen PF: Efficient palliation of haemorrhaging malignant melanoma skin metastases by electrochemotherapy. Melanoma Res 10: 585-589, 2000
5. Moriarty JM, Xing M, Loh CT: Particle embolization to control life-threatening hemorrhage from a fungating locally advanced breast carcinoma: A case report. J Med Case Rep 6:186, 2012
6. Wu CY, Chang CC, Chang HC: Erythematous painful nodules on the scalp and ulcerative nodules on the back of a 49-year-old woman. Dermatol Sinica 26:43-44, 2008
7. Shimozuma K, Sonoo H, Ichihara K: Analysis of the factors influencing the quality of life of patients with advanced or recurrent breast cancer. Surg Today 25:874-882, 1995
8. Richtig E, Ludwig R, Kerl H, et al: Organ- and treatment-specific local response rates to systemic

and local treatment modalities in stage IV melanoma. Br J Dermatol 153:925-931, 2005

9. Mali B, Jarm T, Snoj M, et al: Antitumor effectiveness of electrochemotherapy: A systematic review and meta-analysis. Eur J Surg Oncol 39:4-16, 2013

10. Campana LG, Mocellin S, Basso M, et al: Bleomycin-based electrochemotherapy: Clinical outcome from a single institution's experience with 52 patients. Ann Surg Oncol 16:191-199, 2009

11. Sersa G, Stabuc B, Cemazar M, et al: Electrochemotherapy with cisplatin: The systemic antitumour effectiveness of cisplatin can be potentiated locally by the application of electric pulses in the treatment of malignant melanoma skin metastases. Melanoma Res 10: 381-385, 2000

12. Lai YL, Chang HH, Huang MJ, et al: Combined effect of topical arsenic trioxide and radiation therapy on skin-infiltrating lesions of breast cancer: A pilot study. Anticancer Drugs 14:825-828, 2003

13. Bourke M, Salwa S, Sadadcharam M, et al: Electrochemotherapy for the treatment of intractable cutaneous lesions secondary to breast cancer. Eur J Surg Oncol 37:1011, 2011

14. Kis E, Oláh J, Ócsai H, et al: Electrochemotherapy of cutaneous metastases of melanoma: A case series study and systematic review of the evidence. Dermatol Surg 37:816-824, 2011

15. Hartsell WF, Scott CB, Bruner DW, et al: Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. J Natl Cancer Inst 97:798-804, 2005

16. Sze WM, Shelley M, Held I, et al: Palliation of metastatic bone pain: Single fraction versus multifraction radiotherapy—A systematic review of the randomised trials. Cochrane Database Syst Rev 2:CD004721, 2004

17. Patchell RA, Tibbs PA, Regine WF, et al: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: A randomised trial. Lancet 366: 643-648, 2005

18. Andrews DW, Scott CB, Sperduto PW, et al: Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. Lancet 363:1665-1672, 2004

19. Hofmann MA, Kors C, Audring H, et al: Phase 1 evaluation of intralesionally injected TLR9-agonist PF-3512676 in patients with basal cell carcinoma or metastatic melanoma. J Immunother 31:520-527, 2008

20. Thompson JF, Hersey P, Wachter E: Chemoablation of metastatic melanoma using intralesional Rose Bengal. Melanoma Res 18:405-411, 2008

21. Campana LG, Valpione S, Falci C, et al: The activity and safety of electrochemotherapy in persistent chest wall recurrence from breast cancer after mastectomy: A phase-II study. Breast Cancer Res Treat 134:1169-1178, 2012

22. Kendler M, Micheluzzi M, Wetzig T, et al: Electrochemotherapy under tumescent local anesthesia for the treatment of cutaneous metastases. Dermatol Surg 39:1023-1032, 2013

23. Marty M, Sersa G, Garbay JR, et al: Electrochemotherapy - An easy, highly effective and safe treatment of cutaneous and subcutaneous metastases: Results of ESOPE (European Standard Operating Procedures of Electrochemotherapy) study. Eur J Cancer Suppl 4:3-13, 2006

24. Leonard R, Hardy J, van Tienhoven G, et al: Randomized, double-blind, placebo-controlled, multicenter trial of 6% miltefosine solution, a topical chemotherapy in cutaneous metastases from breast cancer. J Clin Oncol 19:4150-4159, 2001

25. Bedikian AY, Richards J, Kharkevitch D, et al: A phase 2 study of high-dose Allovectin-7 in patients with advanced metastatic melanoma. Melanoma Res 20:218-226, 2010

26. Weide B, Derhovanessian E, Pflugfelder A, et al: High response rate after intratumoral treatment with interleukin-2: Results from a phase 2 study in 51 patients with metastasized melanoma. Cancer 116:4139-4146, 2010

27. Unger C, Sindermann H, Peukert M, et al: Hexadecylphosphocholine in the topical treatment of skin metastases in breast cancer patients. Prog Exp Tumor Res 34:153-159, 1992

28. Byrne CM, Thompson JF, Johnston H, et al: Treatment of metastatic melanoma using electroporation therapy with bleomycin (electrochemotherapy). Melanoma Res 15:45-51, 2005

29. Gaudy C, Richard MA, Folchetti G, et al: Randomized controlled study of electrochemotherapy in the local treatment of skin metastases of melanoma. J Cutan Med Surg 10:115-121, 2006

30. Matthiessen LW, Chalmers RL, Sainsbury DC, et al: Management of cutaneous metastases using electrochemotherapy. Acta Oncol 50:621-629, 2011

31. Unger C, Herrmann R, Berdel WE, et al: Topically applied miltefosine (hexadecylphosphocholine) in patients with skin-metastasized breast cancer. A phase II study. Onkologie 16:170-173, 1993

32. Terwogt JM, Mandjes IA, Sindermann H, et al: Phase II trial of topically applied miltefosine solution in patients with skin-metastasized breast cancer. Br J Cancer 79:1158-1161, 1999

33. Smorenburg CH, Seynaeve C, Bontenbal M, et al: Phase II study of miltefosine 6% solution as topical treatment of skin metastases in breast cancer patients. Anticancer Drugs 11:825-828, 2000

34. Eilender D, LoRusso P, Thomas L, et al: 4,4′-Dihydroxybenzophenone-2,4-dinitrophenylhydrazone (A-007): A topical treatment for cutaneous metastases from malignant cancers. Cancer Chemother Pharmacol 57:719-726, 2006

35. Menéndez PR, Roth BM, Pereira MD, et al: BNCT for skin melanoma in extremities: Updated Argentine clinical results. Appl Radiat Isot 67:S50-S53, 2009

36. Overgaard J, von der Maase H, Overgaard M: A randomized study comparing two high-dose per fraction radiation schedules in recurrent or metastatic malignant melanoma. Int J Radiat Oncol Biol Phys 11:1837-1839, 1985

37. Cascinelli N, Clemente C, Bufalino R, et al: Perinodular injection of thymopentin (TP5) in cutaneous and subcutaneous metastases of melanoma. Melanoma Res 3:471-476, 1993

38. Green DS, Bodman-Smith MD, Dalgleish AG, et al: Phase I/II study of topical imiquimod and intralesional interleukin-2 in the treatment of accessible metastases in malignant melanoma. Br J Dermatol 156:337-345, 2007

39. Li X, Naylor MF, Le H, et al: Clinical effects of in situ photoimmunotherapy on late-stage melanoma patients: A preliminary study. Cancer Biol Ther 10:1081-1087, 2010

40. Salazar LG, Lu H, Gray H, et al: Phase II study of topical imiquimod and abraxane for treatment of breast cancer cutaneous metastases. Cancer Res 71, 2011 (suppl; poster P1-13-04)

41. Florin V, Desmedt E, Vercambre-Darras S, et al: Topical treatment of cutaneous metastases of malignant melanoma using combined imiquimod and 5-fluorouracil. Invest New Drugs 30:1641-1645, 2012

42. Adams S, Kozhaya L, Martiniuk F, et al: Topical TLR7 agonist imiquimod can induce immune-mediated rejection of skin metastases in patients with breast cancer. Clin Cancer Res 18:6748-6757, 2012

43. Plesnicar S, Rudolf Z: Combined BCG and irradiation treatment of skin metastases originating from malignant melanoma. Cancer 50:1100-1106, 1982

44. Heller R, Jaroszeski MJ, Glass LF, et al: Phase I/II trial for the treatment of cutaneous and subcutaneous tumors using electrochemotherapy. Cancer 77:964-971, 1996

45. Rodriguez-Cuevas S, Barroso-Bravo S, Almanza-Estrada J, et al: Electrochemotherapy in primary and metastatic skin tumors: Phase II trial using intralesional bleomycin. Arch Med Res 32: 273-276, 2001

46. Quaglino P, Mortera C, Osella-Abate S, et al: Electrochemotherapy with intravenous bleomycin in the local treatment of skin melanoma metastases. Ann Surg Oncol 15:2215-2222, 2008

47. Benevento R, Santoriello A, Perna G, et al: Electrochemotherapy of cutaneous metastastes from breast cancer in elderly patients: A preliminary report. BMC Surg 12:S6, 2012

48. Sperduto PW, DeLaney TF, Thomas G, et al: Photodynamic therapy for chest wall recurrence in breast cancer. Int J Radiat Oncol Biol Phys 21:441-446, 1991

49. Cairnduff F, Stringer MR, Hudson EJ, et al: Superficial photodynamic therapy with topical 5-aminolaevulinic acid for superficial primary and secondary skin cancer. Br J Cancer 69:605-608, 1994

50. Baas P, van Geel IP, Oppelaar H, et al: Enhancement of photodynamic therapy by mitomycin C: A preclinical and clinical study. Br J Cancer 73:945-951, 1996

51. Kaplan MJ, Somers RG, Greenberg RH, et al: Photodynamic therapy in the management of metastatic cutaneous adenocarcinomas: Case reports from phase 1/2 studies using tin ethyl etiopurpurin (SnET2). J Surg Oncol 67:121-125, 1998

52. Mang TS, Allison R, Hewson G, et al: A phase II/III clinical study of tin ethyl etiopurpurin (Purlytin)-induced photodynamic therapy for the treatment of recurrent cutaneous metastatic breast cancer. Cancer J Sci Am 4:378-384, 1998

53. Cohen MH, Jessup JM, Felix EL, et al: Intralesional treatment of recurrent metastatic cutaneous malignant melanoma: A randomized prospective study of intralesional Bacillus Calmette-Guerin versus intralesional dinitrochlorobenzene. Cancer 41: 2456-2463, 1978

54. Nathanson L, Schoenfeld D, Regelson W, et al: Prospective comparison of intralesional and multipuncture BCG in recurrent intradermal melanoma. Cancer 43:1630-1635, 1979

55. Stewart AK, Lassam NJ, Quirt IC, et al: Adenovector-mediated gene delivery of interleukin-2 in metastatic breast cancer and melanoma: Results of a phase 1 clinical trial. Gene Ther 6:350-363, 1999

56. Hoeller C, Jansen B, Heere-Ress E, et al: Perilesional injection of r-GM-CSF in patients with cutaneous melanoma metastases. J Invest Dermatol 117:371-374, 2001

57. Stopeck AT, Jones A, Hersh EM, et al: Phase II study of direct intralesional gene transfer of allovectin-7, an HLA-B7/beta2-microglobulin DNA-liposome complex, in patients with metastatic melanoma. Clin Cancer Res 7:2285-2291, 2001

58. Radny P, Caroli UM, Bauer J, et al: Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. Br J Cancer 89: 1620-1626, 2003

59. Oratz R, Hauschild A, Sebastian G, et al: Intratumoral cisplatin/adrenaline injectable gel for the treatment of patients with cutaneous and soft tissue metastases of malignant melanoma. Melanoma Res 13:59-66, 2003

60. Triozzi PL, Allen KO, Carlisle RR, et al: Phase I study of the intratumoral administration of recombinant canarypox viruses expressing B7.1 and interleukin 12 in patients with metastatic melanoma. Clin Cancer Res 11:4168-4175, 2005

61. Gonzalez R, Hutchins L, Nemunaitis J, et al: Phase 2 trial of Allovectin-7 in advanced metastatic melanoma. Melanoma Res 16:521-526, 2006

62. Kimata H, Imai T, Kikumori T, et al: Pilot study of oncolytic viral therapy using mutant herpes simplex virus (HF10) against recurrent metastatic breast cancer. Ann Surg Oncol 13:1078-1084, 2006

63. Dummer R, Rochlitz C, Velu T, et al: Intralesional adenovirus-mediated interleukin-2 gene transfer for advanced solid cancers and melanoma. Mol Ther 16:985-994, 2008

64. National Cancer Institute: Levels of Evidence for Adult and Pediatric Cancer Treatment Studies: Strength of Study Design. http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/HealthProfessional/page2

65. Jadad AR, Moore RA, Carroll D, et al: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 17:1-12, 1996

66. Duval S, Tweedie R: Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 56:455-463, 2000

67. Peppercorn JM, Smith TJ, Helft PR, et al: American Society of Clinical Oncology statement: Toward individualized care for patients with advanced cancer. J Clin Oncol 29:755-760, 2011

68. Temel JS, Greer JA, Muzikansky A, et al: Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 363:733-742, 2010

69. Cutaneous metastases, in Bolognia JL, Jorizzo JL, Schaffer JV (eds): Dermatology (ed 3). Philadelphia, PA, Elsevier Saunders, 2012, pp 2049-2055

70. Mir LM, Gehl, J, Sersa G, et al: Standard operating procedures of the electrochemotherapy: Instructions for the use of bleomycin or cisplatin administered either systemically or locally and electric pulses delivered by the Cliniporator by means of invasive or non-invasive electrodes. EJC Supplement 4:14-25, 2006

71. Miklavčič D, Serša G, Brecelj E, et al: Electrochemotherapy: Technological advancements for efficient electroporation-based treatment of internal tumors. Med Biol Eng Comput 50:1213-1225, 2012

72. Fayter D, Corbett M, Heirs M, et al: A systematic review of photodynamic therapy in the treatment of pre-cancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. Health Technol Assess 14:1-288, 2010

73. Sze WM, Sheeley M, Held I: Palliation of metastatic bone pain: Single fraction versus multifraction radiotherapy—A systematic review of the randomised trials. Cochrane Database Syst Rev 2:CD004721, 2004

74. Mali B, Miklavcic D, Campana LG, et al: Tumor size and effectiveness of electrochemotherapy. Radiol Oncol 47:32-41, 2013

75. Howard JH, Thompson JF, Mozzillo N, et al: Metastasectomy for distant metastatic melanoma: Analysis of data from the first Multicenter Selective Lymphadenectomy Trial (MSLT-I). Ann Surg Oncol 19:2547-2555, 2012

76. Ollila DW: Complete metastasectomy in patients with stage IV metastatic melanoma. Lancet Oncol 7:919-924, 2006

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Appendix

Table A1. Patient and Skin Metastasis Details

Study	Year	Local Therapy	No. of Patients With Evaluable Skin Metastases	No. of Lesions	Age (years)		Sex		Metastasis				
												Size	
					Median	Range	M	F	Histology	Location	No.	Median	Range
Heller et al*	1996	ECT	3	10	50	45-65	1	2	Melanoma	Upper extremities Lower extremities	1 2	NA	18-233.6 mm^2
Heller et al*	1996	ECT	1	2	57	57	0	1	Adenocarcinoma of unknown primary	Torso/buttock	1	NA	75.6-98.6 mm^2
Sersa et al	2000	ECT†	9	27	NA	NA	5	4	Melanoma	NA		1,010 mm^3‡	Estimated 600-1,500 μL
Rodriguez-Cuevas et al*	2001	ECT	2	13	59‡	NA	NA	NA	Melanoma	NA		10.3 mm‡	Estimated 5-15 mm
Rodriguez-Cuevas et al*	2001	ECT	2	14	52.5‡	NA	0	2	Breast	NA		21.3 mm‡	Estimated 8-34 mm
Rodriguez-Cuevas et al*	2001	ECT	2	2	62‡	NA	0	2	SCC (upper aerodigestive tract)	NA		27.5 mm‡	Estimated 16-38 mm
Byrne et al	2005	ECT	16	53	75‡	45-86	10	6	Melanoma	Neck Torso/buttock Upper extremities Lower extremities Non-randomized lesion locations not known	1 2 2 12	36 mm^2	9-1,400 mm^2
Gaudy et al	2006	ECT†	12	24	62‡	49-77	NA	NA	Melanoma	NA		10 mm	3-26 mm
Marty et al	2006	ECT	41	171	66	37-91	11	30	Melanoma (49%) Carcinoma (46%) Sarcoma (5%)	Scalp, face, neck Torso/buttock Upper extremities/ lower extremities	13 81 77	< 30 mm	NA
Quaglino et al	2008	ECT	14	233	61	49-77	NA	NA	Melanoma	NA		7-15 mm	2-75 mm
Matthiessen et al	2011	ECT	24	94	69.6	38.9-94.7	NA	NA	Melanoma (40%) Breast (29%) Other (31%)	NA		12 mm	1-200 mm
Benevento et al	2012	ECT	12	142	76	NA	1	11	Breast	NA		5-10 mm	5 to > 30 mm
Campana et al	2012	ECT	35	35	NA		0	35	Breast	Torso/buttock	35	20 mm	10-220 mm
Kendler et al*	2013	ECT	2	50	81.5	75-88	1	1	Melanoma	Lower extremities	40	145.5 cm^2	135-156 cm^2
Kendler et al*	2013	ECT	1	29	80	80	0	1	Breast	Torso/buttock	29	163 cm^2	128-198 cm^2
Sperduto et al	1991	PDT	20	20	55.5	39-76	0	20	Breast	Torso/buttock	20	NA	2 mm to > 5 cm
Cairnduff et al	1994	PDT	5	14	NA	NA	0	5	Breast	NA		11 mm	10-75 mm
Baas et al	1996	PDT†	4	20	49.5	45-74	0	4	Breast	Torso/buttock	20	NA	NA
Kaplan et al	1998	PDT	3	13	63	62-64	0	3	Adenocarcinoma (submandibular gland, colon, breast)	Face Torso/buttock	1 2	NA	NA
Mang et al	1998	PDT	8	86	65	40-71	0	8	Breast	Torso/buttock	86		3-45 mm
Overgaard et al	1985	RT	NA	15	NA		NA	NA	Melanoma	Torso/buttock Upper extremities Lower extremities	5 3 7	2 cm^2	1-12 cm^2
Menendez et al	2009	RT	7	88	64	51-74	1	6	Melanoma	Lower extremities	88	NA	NA

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Table A1. Patient and Skin Metastasis Details (continued)

Study	Year	Local Therapy	No. of Patients With Evaluable Skin Metastases	No. of Lesions	Age (years)		Sex		Metastasis				
												Size	
					Median	Range	M	F	Histology	Location	No.	Median	Range
Cohen§	1978	ILT	9	199	48	27-58	4	5	Melanoma	Scalp	1	NA	NA
										Torso/buttock	1		
										Upper extremities	2		
										Lower extremities	5		
Cohen§	1978	ILT	9	567	42	24-68	5	4	Melanoma	Scalp	1	NA	NA
										Upper extremities	1		
										Lower extremities	7		
Nathanson et al	1979	ILT	22	22	51-60 (range)	40 to > 70	13	9	Melanoma	Scalp, face, neck	5	< 20 mm	NA
										Torso/buttock	3		
										Upper extremities	2		
										Lower extremities	10		
										Unknown	2		
Cascinelli et al	1993	ILT	16	47	NA	NA	NA	NA	Melanoma	NA		NA	NA
Stewart et al*	1999	ILT	8	8	NA	NA	0	8	Breast	NA		NA	NA
Stewart et al*	1999	ILT	15	15	NA	NA	NA	NA	Melanoma	NA		NA	NA
Hoeller et al	2001	ILT	29	29	49	29-84	25	27	Melanoma	NA		6.1 cm^2	0.7-24 cm^2
Stopeck et al	2001	ILT	7	7	76.4‡	45-90	5	2	Melanoma	NA		NA	NA
Radny et al	2003	ILT	25	244	61	39-82	13	12	Melanoma	Scalp	9	0.3 cm^2	0.01-100 cm^2
										Face	8		
										Neck	7		
										Torso/buttock	52		
										Upper extremities	17		
										Lower extremities	153		
Oratz et al	2003	ILT	23	237	59.2	19-83	10	14	Melanoma	NA		NA	< 5 mm to > 20 mm
Byrne et al	2005	ILT	16	19	75‡	45-86	10	6	Melanoma	Neck	1	30 mm^2	20-2,500 mm^2
										Torso/buttock	2		
										Upper extremities	1		
										Lower extremities	15		
Triozzi et al	2005	ILT	NA	14	63	34-83	8	6	Melanoma	NA		NA	NA
Gonzalez et al	2006	ILT	12	16	62‡	49-77	NA	NA	Melanoma	NA		10 mm	4-18 mm
Kimata et al	2006	ILT	77	77	57.7‡	33-82	46	31	Melanoma	NA		< 25 cm^2	NA
Gaudy et al	2006	ILT†	6	5	64	48-76	0	6	Breast	NA		NA	NA
Dummer et al	2008	ILT†	25	25	59	22-86	14	11	Melanoma	NA		NA	NA
Hofmann et al	2008	ILT	5	5	64	27-70	4	1	Melanoma	Scalp	1	0.82 cm^2	0.12-16.65 cm^2
										Torso/buttock	4		
Thompson et al	2008	ILT	11	26	83	75-86	4	7	Melanoma	Face	1	0.29 cm^3	0.02-12.8 cm^3
										Lower extremities	25		
Bedikian et al	2010	ILT	85	255	60	26-98	69	58	Melanoma	NA		NA	≥ 1 to ≤ 25 cm^2
Weide et al	2010	ILT	48	894	69	37-88	21	27	Melanoma	NA		NA	NA
Unger et al	1992	TT	24	24	55	39-85	0	24	Breast	Torso/buttock	24	NA	NA
Unger et al	1993	TT†	52	52	59	NA	0	52	Breast	Torso/buttock	52	NA	NA
Terwogt et al	1999	TT	30	30	57	30-90	0	30	Breast	Torso/buttock	30	NA	NA
Smorenburg et al	2000	TT†	18	18	61	43-79	0	18	Breast	Torso/buttock	18	NA	NA
Leonard et al	2001	TT†	24	19	68‡	39-86	0	19	Breast	Torso/buttock	19	NA	NA

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Table A1. Patient and Skin Metastasis Details (continued)

Study	Year	Local Therapy	No. of Patients With Evaluable Skin Metastases	No. of Lesions	Age (years)		Sex		Metastasis				
												Size	
					Median	Range	M	F	Histology	Location	No.	Median	Range
Eilender et al*	2006	TT†	12	12	NA	NA	NA	NA	Breast	Scalp	1	47.35 cm^2	1.4-1,596 cm^2
										Neck	1		
										Torso/buttock	9		
										Upper extremities	1		
Eilender et al*	2006	TT	5	5	NA	NA	NA	NA	Melanoma	Scalp	1	30.16 cm^2	5.75-2,574 cm^2
										Torso/buttock	1		
										Lower extremities	3		
Eilender et al*	2006	TT	2	2	NA	NA	NA	NA	Angiosarcoma	Scalp	2	89.75 cm^2	32.5-147 cm^2
Eilender et al*	2006	TT	4	4	NA	NA	NA	NA	Kaposi's Sarcoma	Face	1	8.48 cm^2	0.5-14.7 cm^2
										Upper extremities	1		
										Lower extremities	2		
Eilender et al*	2006	TT	1	1	NA	NA	NA	NA	Head and neck SCC	Neck	1	42 cm^2	42 cm^2
Salazar et al	2011	TT†	10	10	54	48-92	0	10	Breast	NA		NA	NA
Florin et al	2012	TT	5	45	82	72-88	0	5	Melanoma	Lower extremities	45	NA	NA
Adams et al	2012	TT†	10	10	50	44-71	0	10	Breast	Torso/buttock	10	NA	NA
Plesnicar et al	1982	ILT + RT	19	19	NA	33-80	11	8	Melanoma	Scalp	2	7-35 mm	< 7 to > 35 mm
										Neck	2		
										Torso/buttock	9		
										Lower extremities	8		
										Multiple sites involved for some patients			
Lai et al	2003	TT + RT	7	7	53	33-71	0	7	Breast	Torso/buttock	7	NA	
Green et al	2007	TT + ILT	10	178	58.5	46-80	7	3	Melanoma	Scalp	2	NA	NA
										Face	1		
										Neck	1		
										Torso/buttock	5		
										Upper extremities	3		
										Lower extremities	3		
Li et al	2010	TT + PDT	11	11	69	46-87	7	4	Melanoma	NA		NA	NA

Abbreviations: ECT, electrochemotherapy; ILT, intralesional therapy; NA, not available; PDT, photodynamic therapy; RT, radiotherapy; SCC, squamous cell cancer; TT, topical therapy.
*Study split up by histology.
†Systemic therapy allowed.
‡Mean value rather than median was used.
§Study split up by drug used for ILT injections.

Table A2. Treatment Details

Study	Year	Local Therapy	Local Treatment-Specific Details				Systemic Therapy Details	
							Concurrent Systemic Therapy	Concurrent Therapy Used
			ECT Drug	Route	No. of Treatments	Anesthesia		
Heller et al*	1996	ECT	Bleomycin	IV	1	Local		
Heller et al*	1996	ECT	Bleomycin	IV	1	Local		
Sersa et al	2000	ECT†	Cisplatin	IV	4	Local	100%	Vinblastine, lomustine, and interferon-2β
Rodriguez-Cuevas et al*	2001	ECT	Bleomycin	IL	1-4	Local		
Rodriguez-Cuevas et al*	2001	ECT	Bleomycin	IL	1	Local		
Rodriguez-Cuevas et al*	2001	ECT	Bleomycin	IL	1-4	Local		
Byrne et al	2005	ECT	Bleomycin	IL	1	Local plus oral sedative needed		
Gaudy et al	2006	ECT	Bleomycin	IL	1	Local	80%	Dacarbazine (n = 3), fotemustine (n = 4), vindesine (n = 1)
Marty et al	2006	ECT	Bleomycin or cisplatin	Bleomycin, IV or IL; cisplatin, IL	1	General or local		
Quaglino et al	2008	ECT	Bleomycin	IV	Median, 1; range, 1-3	General		
Matthiessen et al	2011	ECT	Bleomycin	IL or IV	Median, 1; range, 1-2	55% general, 45% local		
Benevento et al	2012	ECT	Bleomycin	IV	Median, 1; range, 1-3	General		
Campana et al	2012	ECT	Bleomycin	IV	1 (outcomes reported after first treatment)	General		
Kendler et al*	2013	ECT	Bleomycin	IL	1	Local		
Kendler et al*	2013	ECT	Bleomycin	IL	1	Local		
			PDT Laser Used	Photosensitizer	No. of Applications	Anesthesia		
Sperduto et al	1991	PDT	Argon dye laser	Dihematoporphyrin ether	Median, 3; range, 1-10			
Cairnduff et al	1994	PDT	Copper vapor/dye laser	ALA	1	Local		
Baas et al	1996	PDT†	Argon dye laser	Porfimer sodium	1		35%	Mitomycin
Kaplan et al	1998	PDT	Dye laser powered by potassium titanyl phosphate laser	Tin ethyl etiopurpurin	1	Local		
Mang et al	1998	PDT	Diode laser or potassium titanyl phosphate laser: yttrium argon garnet dye laser	Tin ethyl etiopurpurin	1			
			Type of RT		No. of Fractions	Fractions/Week		
Overgaard et al	1985	RT	MV electrons or photons		Median, 3; range, 3-5	2		
Menendez et al	2009	RT	Boron-neutron capture therapy		Median, 1; range, 1-3			
			IL Drug	No. of Treatments	Frequency of Dosing	Anesthesia		
Cohen et al‡	1978	ILT	Bacille Calmette-Guérin	1-2	Every 4-6 weeks			
Cohen et al‡	1978	ILT	Dinitrochlorobenzene	1-2	Every 4-6 weeks			
Nathanson et al	1979	ILT	Bacille Calmette-Guérin	6	Once per week			
Cascinelli et al	1993	ILT	Thymopoietin pentapeptide	6	3 times per week			
Stewart et al*	1999	ILT	Interleukin-2 adenovirus	1-2	NA			
Stewart et al*	1999	ILT	Interleukin-2 adenovirus	1-5	NA			
Hoeller et al	2001	ILT	Granulocyte-macrophage colony-stimulating factor	10	Daily for 5 days, then cycle repeated after 21 days			
Stopeck et al	2001	ILT	Allovectin-7	6	Once per week			

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Table A2. Treatment Details (continued)

Study	Year	Local Therapy	Local Treatment-Specific Details				Systemic Therapy Details: Concurrent Systemic Therapy	Systemic Therapy Details: Concurrent Therapy Used
Radny et al	2003	ILT	Interleukin-2	Mean of 10 per lesion	2-3 times per week for 1-12 weeks			
Oratz et al	2003	ILT	Cisplatin + adrenaline	Median, 5; maximum, 43	Once per week			
Byrne et al	2005	ILT	Bleomycin	1	Once	Local		
Triozzi et al	2005	ILT	B7.1 (ALVAC)	4	Twice per week			
Gonzalez et al	2006	ILT	Alovectin-7	6-18	Once per week			
Kimata et al	2006	ILT	HF10 (oncolytic herpes simplex virus-1 mutant)	1-3	Once only or once per day × 3 days			
Gaudy et al	2006	ILT†	Bleomycin	1	Once	Local	80%	NA
Dummer et al	2008	ILT†	Interleukin-2 adenovirus	2-20	Every 1-3 weeks		24%	NA
Hofmann et al	2008	ILT	Toll-like receptor 9 agonist	5	Every 2 weeks			
Thompson et al	2008	ILT	Rose Bengal					
Bedikian et al	2010	ILT	Allovectin-7	6	Once per week			
Weide et al	2010	ILT	Interleukin-2	6-12	3 times per week			
			TT Drug	Frequency	Duration of Treatment			
Unger et al	1992	TT	Miltefosine	1-2 times per day	> 8 weeks			
Unger et al	1993	TT†	Miltefosine	1-2 times per day	> 8 weeks		58%	Hormonal or chemotherapy
Terwogt et al	1999	TT	Miltefosine	1-2 times per day	Median, 10 weeks; range, 1-68 weeks			
Smorenburg et al	2000	TT†	Miltefosine	1-2 times per day	Median, 10.5 weeks; range, 3-46 weeks		89%	Hormonal or chemotherapy
Leonard et al	2001	TT†	Miltefosine	1-2 times per day	Median, 8.5 weeks; range, 2-33 weeks		10%	Hormone therapy
Eilender et al*	2006	TT†	4,4′-Dihydroxybenzophenone-2, 4-dinitrophenylhydrazone	Twice per day	Median, 11 weeks; range, 2-17 weeks		100%	Hormone therapy
Eilender et al*	2006	TT	4,4′-Dihydroxybenzophenone-2, 4-dinitrophenylhydrazone	Twice per day	Median, 6 weeks; range, 4-20 weeks			
Eilender et al*	2006	TT	4,4′-Dihydroxybenzophenone-2, 4-dinitrophenylhydrazone	Twice per day	3 weeks			
Eilender et al*	2006	TT	4,4′-Dihydroxybenzophenone-2, 4-dinitrophenylhydrazone	Twice per day	Median, 13 weeks; range, 2-17 weeks			
Eilender et al*	2006	TT	4,4′-Dihydroxybenzophenone-2, 4-dinitrophenylhydrazone	Twice per day	4 weeks			
Salazar et al	2011	TT†	Imiquimod	4 days/week	4-12 weeks		100%	Abraxane
Florin et al	2012	TT	Imiquimod and fluorouracil	5 days per week	Median, 21 months; range, 3-27 months			
Adams et al	2012	TT†	Imiquimod	5 days per week	8 weeks		70%	Hormonal or chemotherapy
			Combination Therapy 1		Combination Therapy 2			
Plesnicar et al	1982	ILT + RT	ILT: one treatment with Bacille Calmette-Guérin		RT: 13-39 Gy in 4.3-8.6 Gy fractions for 3-9 fractions 1-2 days per week			
Lai et al	2003	TT + RT	TT: arsenic gel, 5 days/week for 2-5 weeks		RT: 30-50 Gy in 2-3 Gy fractions for 10-25 fractions 5 days per week			
Green et al	2007	TT + ILT	TT: imiquimod nightly for first 8 weeks for > 2 months		ILT: interleukin-2 every 2 weeks for > 6 months			
Li et al	2010	TT + PDT	TT: imiquimod twice per day for 6 weeks (84 treatments)		PDT: 805-nm diode laser with indocyanine green every 2 weeks for two sessions			

Abbreviations: ECT, electrochemotherapy; IL, intralesional; ILT, intralesional therapy; IV, intravenous; NA, not available; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy.
*Study split by histology if toxicity information was extractable by histology.
†Systemic therapy allowed.
‡Study split up by drug used for IL injections.

Table A3. Additional Response Details

Study	Year	Local Therapy	No. of Lesions	PR		SD		PD	
				No.	Definition Used	No.	Definition Used	No.	Definition Used
Heller et al*	1996	ECT	10	2	50% reduction in tumor volume	0	NA	5	"No effect"
Heller et al*	1996	ECT	2	0	50% reduction in tumor volume	0	NA	0	"No effect"
Sersa et al	2000	ECT†	27	10	> 50% reduction in tumor volume	11	< 25% increase or < 50% reduction in tumor volume	3	> 25% increase in tumor volume
Rodriguez-Cuevas et al*	2001	ECT	13	8	As listed	0	NA	2	"No response"
Rodriguez-Cuevas et al*	2001	ECT	14	6	As listed	0	NA	0	"No response"
Rodriguez-Cuevas et al*	2001	ECT	2	2	As listed	0	NA	0	"No response"
Byrne et al	2005	ECT	53	5	> 50% reduction in tumor area	9	Did not meet criteria for CR, PR, or PD	5	> 25% increase in lesion size
Gaudy et al	2006	ECT†	24	3	> 50% reduction in tumor area	3	Not meeting criteria for CR, PR, or PD	1	> 25% increase in tumor volume
Marty et al	2006	ECT	171	19	WHO 1997; > 50% reduction in diameter for ≥ 4 weeks	18	WHO 1997; ≤ 25% increase or < 50% reduction in tumor diameter	8	WHO 1997; > 25% increase in tumor diameter
Quaglino et al	2008	ECT	233	80	WHO 1997; > 50% reduction in tumor area for at least 4 weeks	17	WHO 1997; < 25% increase or < 50% reduction in tumor area	0	> 25% increase in tumor area
Matthiessen et al	2011	ECT	94	18	RECIST v1 2000; ≥ 30% decrease in target lesion	11	RECIST v1 2000; < 20% increase or < 30% decrease in target lesion	7	RECIST v1 2009; ≥ 20% increase in target lesion
Benevento et al	2012	ECT	142	24	RECIST v1 2000	11	RECIST v1 2000; SD + NC	0	RECIST v1 2000
Campana et al	2012	ECT	35	13	RECIST v1 2000	3	RECIST v1 2000	0	RECIST v1 2000
Kendler et al*	2013	ECT	50	0	RECIST 2009; ≥ 30% decrease in tumor area	23	< 20% increase or < 30% decrease in tumor area	22	≥ 20% increase in tumor area or an absolute increase of 5 mm
Kendler et al*	2013	ECT	29	0	RECIST 2009; ≥ 30% decrease in tumor area	22	< 20% increase or < 30% decrease in tumor area	0	≥ 20% increase in tumor area or an absolute increase of 5 mm
Sperduto et al	1991	PDT	20	9	> 50% reduction in measurable nodules or a complete clinical regression with residual microscopic disease	0	NA	7	"No response: < 50% response, no change, or progression of disease"
Cairnduff et al	1994	PDT	14	0	50% reduction in tumor size	0	NA	9	"No other responses were seen"
Baas et al	1996	PDT†	20	3	As listed	0	NA	2	"No change"‡
Kaplan et al	1998	PDT	13	0	NA	0	NA	0	NA
Mang et al	1998	PDT	86	7	As listed	0	NA	0	NA
Overgaard et al	1985	RT	15	5	> 50% reduction in tumor area	0	< 25% progression or < 50% reduction in tumor area	0	> 25% progression of tumor area
Menendez et al	2009	RT	88	9	"Partial response"	27	"No change"	0	All lesions had either CR, PR, or SD‡
Cohen et al	1978	ILT	766	NA	NA	NA	NA	119	Did not regress
Nathanson et al	1979	ILT	22	7	≥ 50% decrease in diameters for minimum of 2 weeks	1	Listed as no change	11	≥ 50% increase in diameters
Cascinelli et al	1993	ILT	47	NA	NA	NA	NA	23	Did not have an "objective response"‡
Stewart et al*	1999	ILT	8	NA	NA	NA	NA	6	"No response"
Stewart et al*	1999	ILT	15	NA	NA	NA	NA	10	"No response"
Hoeller et al	2001	ILT	29	2	≥ 50% reduction in size with no new lesions	10	< 25% increase in size or < 25% decrease in size	9	
Stopeck et al	2001	ILT	7	3	> 50% regression of tumor size‡	1	≤ 25% increase or ≤ 50% decrease in tumor size‡	1	> 25% increase in tumor size‡
Radny et al	2003	ILT	244	16	≥ 50% tumor volume regression	NA	≤ 25% increase or < 50% decrease in volume	NA	NA

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Table A3. Additional Response Details (continued)

Study	Year	Local Therapy	No. of Lesions	PR		SD		PD	
				No.	Definition Used	No.	Definition Used	No.	Definition Used
Oratz et al	2003	ILT	237	21	> 50% decrease in sum of diameters	0	NA	7	"Progression"
Byrne et al	2005	ILT	19	1	> 50% reduction in tumor area	3	Did not meet criteria for CR, PR, or PD	10	> 25% increase in lesion size
Triozzi et al	2005	ILT	14	0	≥ 50% reduction in volume	2	< 25% increase or < 25% decrease in volume	12	≥ 25% increase in volume
Gonzalez et al	2006	ILT	16	4	> 50% reduction in tumor area	3	Not meeting criteria for CR, PR, or PD	3	> 25% increase in tumor volume
Kimata et al	2006	ILT	77	5	WHO; ≥ 50% reduction in area	18	WHO classification; < 25% increase or < 50% decrease in tumor area	52	WHO; > 25% increase in size or new lesions
Gaudy et al	2006	ILT†	5	4	Moderate to marked response: marked changes in one third or more of tumor cells	1	Mild response, mild changes in cancer cells or marked changes in less than one third of cancer cells	0	All had CR,PR, or SD‡
Dummer et al	2008	ILT†	25	2	WHO; ≥ 50% reduction in size for ≥ 4 weeks	3	WHO; does not meet definition of CR, PR or PD	16	WHO; > 25% increase in size or new lesions
Hofmann et al	2008	ILT	5	0	NA	1	< 50% reduction in tumor area	3	> 20% increase in tumor area
Thompson et al	2008	ILT	26	3	RECIST JNCI 2000	7	RECIST JNCI 2000	6	NA
Bedikian et al	2010	ILT	255	11	RECIST JNCI 2000	32	RECIST JNCI 2000	80	NA
Weide et al	2010	ILT	894	6	≥30% decrease in greatest single dimension	146	< 20% increase or < 30% decrease in greatest single dimension	38	≥ 20% increase in greatest single dimension
Unger et al	1992	TT	24	3	"Partial remission"	8	"No change"	9	"Progressive disease"
Unger et al	1993	TT†	52	10	WHO criteria	28	WHO criteria	13	WHO criteria
Terwogt et al	1999	TT	30	6	≥ 50% reduction in tumor size for ≥ 4 weeks	10	< 25% increase or < 50% decrease in tumor size	7	≥ 25% increase in tumor size
Smorenburg et al	2000	TT†	18	4	WHO	7		7	WHO
Leonard et al	2001	TT†	19	6	WHO 1979; ≥ 50% reduction in tumor area	7	< 25% increase or < 50% decrease in tumor area	4	≥ 25% increase in tumor area
Eilender et al*	2006	TT†	12	1	≥ 50% decrease in tumor area	4	< 25% increase or < 50% decrease in tumor area	6	≥ 25 increase in tumor area
Eilender et al*	2006	TT	5	2	≥ 50% decrease in tumor area	0	< 25% increase or < 50% decrease in tumor area	3	≥ 25 increase in tumor area
Eilender et al*	2006	TT	2	1	≥ 50% decrease in tumor area	0	< 25% increase or < 50% decrease in tumor area	1	≥ 25 increase in tumor area
Eilender et al*	2006	TT	4	2	≥ 50% decrease in tumor area	0	< 25% increase or < 50% decrease in tumor area	2	≥ 25 increase in tumor area
Eilender et al*	2006	TT	1	0	≥ 50% decrease in tumor area	0	< 25% increase or < 50% decrease in tumor area	1	≥ 25 increase in tumor area
Salazar et al	2011	TT†	10	4	"Modified WHO criteria"	2	"Modified WHO criteria"	1	"Modified WHO criteria"
Florin et al	2012	TT	45	25	As listed: "partial response"	1	As listed: "stable disease"	0	As listed: "progressive disease"
Adams et al	2012	TT†	10	2	> 50% reduction in tumor area	6	< 25% increase or ≤ 50 reduction in tumor area‡	2	≥ 25% increase in tumor size
Plesnicar et al	1982	ILT + RT	19	1	"Incomplete reduction in volume of metastases"	0	NA	4	"Minimal or no response"‡
Lai et al	2003	TT + RT	7	3	> 50% reduction in tumor area ≥ 4 weeks	1	< 25% increase or < 50% decrease in tumor area	0	≥ 25% increase in tumor area or new lesions in treatment field

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Table A3. Additional Response Details (continued)

Study	Year	Local Therapy	No. of Lesions	PR		SD		PD	
				No.	Definition Used	No.	Definition Used	No.	Definition Used
Green et al	2007	TT + ILT	178	18	≥ 50% reduction in largest diameter	53	Did not meet criteria for CR, PR, or PD	33	Subcutaneous: ≥ 20% increase in largest diameter Cutaneous: any increase in size or pigmentation
Li et al	2010	TT + PDT	11	3	RECIST; ≥ 30% decrease in tumor area	0	< 20% increase or < 30% decrease in tumor area	0	≥ 20% increase in tumor area or appearance of new lesions

Abbreviations: CR, complete response; ECT, electrochemotherapy; ILT, intralesional therapy; JNCI, *Journal of the National Cancer Institute*; NA, not available; NC, no change; PD, progressive disease; PDT, photodynamic therapy; PR, partial response; RT, radiotherapy; SD, stable disease; TT, topical therapy.

*Study split up by histology.

†Systemic therapy allowed.

‡Response definition was not clearly stated, and we implemented the listed definition of response.

Table A4. Recurrence Details

Study	Year	Local Therapy	Recurrence Rate
Heller et al*	1996	ECT	0 of 3
Heller et al*	1996	ECT	0 of 2
Sersa et al	2000	ECT†	NA
Rodriguez-Cuevas et al*	2001	ECT	NA
Rodriguez-Cuevas et al*	2001	ECT	NA
Rodriguez-Cuevas et al*	2001	ECT	NA
Byrne et al	2005	ECT	0 of 17
Gaudy et al	2006	ECT†	2 of 24
Marty et al	2006	ECT	NA
Quaglino et al	2008	ECT	54 of 216
Matthiessen et al	2011	ECT	NA
Benevento et al	2012	ECT	NA
Campana et al	2012	ECT	5 of 35 (additional ECT sessions allowed)
Kendler et al*	2013	ECT	NA
Kendler et al*	2013	ECT	NA
Sperduto et al	1991	PDT	NA
Cairnduff et al	1994	PDT	0 of 5
Baas et al	1996	PDT†	NA
Kaplan et al	1998	PDT	0 of 13
Mang et al	1998	PDT	0 of 86
Overgaard et al	1985	RT	2 of 15
Menendez et al	2009	RT	NA
Cohen et al	1978	ILT	NA
Nathanson et al	1979	ILT	NA
Cascinelli et al	1993	ILT	NA
Stewart et al*	1999	ILT	NA
Stewart et al*	1999	ILT	NA
Hoeller et al	2001	ILT	
Stopeck et al	2001	ILT	NA
Radny et al	2003	ILT	NA
Oratz et al	2003	ILT	NA
Byrne et al	2005	ILT	0 of 19
Triozzi et al	2005	ILT	NA
Gonzalez et al	2006	ILT	0 of 16
Kimata et al	2006	ILT	NA
Gaudy et al	2006	ILT†	NA
Dummer et al	2008	ILT†	NA
Hofmann et al	2008	ILT	NA
Thompson et al	2008	ILT	NA
Bedikian et al	2010	ILT	9 of 15
Weide et al	2010	ILT	NA
Unger et al	1992	TT	NA
Unger et al	1993	TT†	NA
Terwogt et al	1999	TT	NA
Smorenburg et al	2000	TT†	NA
Leonard et al	2001	TT†	NA
Eilender et al*	2006	TT†	NA
Eilender et al*	2006	TT	NA
Eilender et al*	2006	TT	NA
Eilender et al*	2006	TT	NA
Eilender et al*	2006	TT	NA
Salazar et al	2011	TT†	NA
Florin et al	2012	TT	0 of 44
Adams et al	2012	TT†	NA
Plesnicar et al	1982	ILT + RT	NA
Lai et al	2003	TT + RT	NA
Green et al	2007	TT + ILT	NA
Li et al	2010	TT + PDT	NA

Abbreviations: ECT, electrochemotherapy; ILT, intralesional therapy; NA, not available; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy.
*Study split up by histology.
†Systemic therapy allowed.

Table A5. Toxicity Details

Study	Year	Local Therapy	Toxicity Grading Scale Listed	Details of Toxicity by Grade	Grade 3 or Higher or Severe Toxicity	Toxicities Reported	Toxicity Resolution
Heller et al	1996	ECT	NA	NA	0	Muscle contractions during each pulse, mild pain at treatment site during each pulse, slight burning of skin, muscle fatigue, fever, chills, nausea, general malaise by 24 to 48 hours after treatment	Pain resolved by 24 to 48 hours; burning of skin resolved by 2 to 4 weeks
Sersa et al	2000	ECT*	NA	NA	0	Muscle contractions, slight erythema, scab, minimal scarring, slight depigmentation	NA
Rodriguez-Cuevas et al	2001	ECT	NA	NA	0	Muscle contractions (well tolerated), fibrosis	NA
Byrne et al	2005	ECT	CALGB CTC, 1989	NA	0	During ECT: electric shock sensation, muscle spasm, pain. Treated lesions: inflammatory reaction, superficial necrosis, eschar	All healed by 16 weeks post-treatment
Gaudy et al	2006	ECT*	NA	NA	NA	ECT causes discomfort and local pain in nine of 12 patients, and three of 12 myoclonus. Hematoma in two of 12. No systemic toxicity.	"No residual pain after treatment." Complete healing median time, 2 weeks, one patient took 8 months to heal
Marty et al	2006	ECT	NA	NA	None related to treatment	Local pain, muscle contraction (> 78% of patients)	Pain reduced significantly by 2 days post-treatment
Quaglino et al	2008	ECT	NA	NA	0	Erythema, slight edema at treatment site in three patient; marks from electrodes, erosion in all cases	Local erythema resolved within a "few days," and scars healed within 1 month
Matthiessen et al	2011	ECT	CTC v3	NA	"No serious adverse events"; "no CTC grade 3 or 4 toxicity"	Flu-like symptoms (10%), pain for 1 to 2 days post-treatment (10%), ulceration (4%), cough (2%), allergic skin reaction (2%), anxiety (2%)	NA
Benevento et al	2012	ECT	NA	NA	NA	NA	NA
Campana et al	2012	ECT	CTCAE v3.0	Local: grade 1, 20%; grade 2, 23%; grade 3, 14%	Grade 3 ulceration in five of 35 (many had ulcerative metastases at presentation)	Fever (16.1%), uncontrolled pain (5.7%), nausea/vomiting (n = 4), syncope (n = 1), urticaria (n = 1)	77% had pain 7 days after ECT; 49% had pain 1 month after ECT
Kendler et al	2013	ECT	NA	NA	No serious adverse events	Pain requiring medication, cutaneous infection 7 days post-treatment (n = 1), superficial ulceration at 2 weeks (n = 1), burning sensation (n = 1)	Infection resolved within 3 days with antibiotics
Sperduto et al	1991	PDT	NA	NA	One patient needed skin flap	100% had erythema, 95% had pain, 25% had blistering, 50% had necrosis, 20% had ulceration	NA
Cairnduff et al	1994	PDT	NA	NA	0	Sensations and discomfort during treatment including burning, prickling, or boring sensation. Edema, erythema, weeping for 1 to 2 weeks	All healed by 2 to 3 months

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Table A5. Toxicity Details (continued)

Study	Year	Local Therapy	Toxicity Grading Scale Listed	Details of Toxicity by Grade	Grade 3 or Higher or Severe Toxicity	Toxicities Reported	Toxicity Resolution
Baas et al	1996	PDT	NA	NA	0	Bluish/brown discoloration for first 24 hours, turned black with scab over next 10 days and remained for 8 weeks to 20 months. Rare local infection treated with topical or oral antibiotics, one burning sensation.	Most scabs resolved by 20 months
Kaplan et al	1998	PDT	NA	NA	NA	Transient facial swelling, deep eschar, erythema, necrotic lesions requiring debridement	Local swelling and eschar resolved by 1 month
Mang et al	1998	PDT	NA	NA	0	Chest wall pain ranged from 2 days to 3 weeks, one localized infection. Pain managed by oral medication. One patient had photosensitivity. All at 1 month had scab and larger lesions formed an eschar. Cosmetic results were excellent.	Local pain resolved by 3 weeks at the latest
Overgaard et al	1985	RT	Overgaard†	Moderate erythema (n = 7); severe erythema (n = 8)	Eight had severe erythema, but none had moist desquamation	Moderate and severe erythema, fibrosis	NA
Menendez et al	2009	RT	Listed grade 1 to 3 with no definitions	Grade 1, five of seven; grade 3, three of seven	Three of seven had ulceration	Ulceration	NA
Cohen et al‡	1978	ILT	NA	NA	Three grade 4 "near fatality" from DIC	Fever 88%, chills 84%, nausea 40%, major ulceration 44%, cellulitis 16%, distant infection 8%, DIC 12%	NA
Cohen et al‡	1978	ILT	NA	NA	0	Fever 0%, chills 0%, nausea 0%, major ulceration 4%, cellulitis 2%, distant infection 0%, DIC 0%	NA
Nathanson et al	1979	ILT	NA	NA	NA	Vomiting/diarrhea (n = 4), fever (n = 16), skin symptoms (n = 5), moderate leukopenia or thrombocytopenia (n = 4), moderate change in LFTs (n = 2), severe change in LFTs (n = 1)	NA
Cascinelli et al	1993	ILT	NA	NA	NA	NA	NA
Stewart et al§	1999	ILT	Simply listed toxicity by grade 1, 2, 3 but no definition	Grade 2, one patient (pain and fever)	0	Local inflammation, injection site pain, fever, tissue necrosis	Inflammation resolved after 5 to 7 days
Stewart et al§	1999	ILT	Simply listed toxicity by grade 1, 2, 3 but no definition	Grade 2, four patients (pain and fever)	0	Local inflammation, injection site pain, fever, cellulitis, joint pain, nausea, myalgia, hiccups	Inflammation resolved after 5 to 7 days
Hoeller et al	2001	ILT	WHO	Of 51 evaluable patients, 46 had grade 1 toxicity, six grade 2, one grade 3	One had pain at injection site	Pruritus, erythema at injection site, ecchymoses, pain at injection site	NA
Stopeck et al	2001	ILT	NA	NA	NA	Mild drowsiness, local erythema, increase in WBC, increase in eosinophils	NA

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Table A5. Toxicity Details (continued)

Study	Year	Local Therapy	Toxicity Grading Scale Listed	Details of Toxicity by Grade	Grade 3 or Higher or Severe Toxicity	Toxicities Reported	Toxicity Resolution
Radny et al	2003	ILT	NCI CTC v2.0, 1999	Overall: erythema 100%, swelling, necrosis 89%, erosion 75%, ulceration 75%, eschar 71%, bleeding 64%, pain 50%	"Severe": erythema 46%, swelling 36%, necrosis 61%, erosion 21%, ulceration 43%, eschar 43%, bleeding 4%, pain 21%	Erythema, swelling, necrosis, erosion, ulceration, eschar, bleeding, pain	6 to 31 weeks for resolution of local symptoms
Oratz et al	2003	ILT	WHO Criteria	Grade 1, 100%; grade 2, 54%; grade 3, 4%	Grade 3, 4% (n = 1) severe headache	Local erythema, fever, flu-like symptoms, pain, fatigue, nausea/vomiting, stomach pain, diarrhea, headache, muscle cramps, tachycardia	All had local erythema that resolved within days of treatment
Byrne et al	2005	ILT	CALGB CTC 1989	NA	NA	Treated lesions: inflammatory reaction, superficial necrosis, eschar	All healed by 16 weeks post-treatment
Triozzi et al	2005	ILT	NCI CTC v2.0	23 grade 1; 19 grade 2; zero grade 3 to 4	0	Inflammatory reactions at injection site, fever, chills, myalgia, fatigue, superficial vesicles/bullae	NA
Gonzalez et al	2006	ILT	NA	NA	NA	NA	NA
Kimata et al	2006	ILT	WHO 1979	95% grade 1 or 2	One grade 3 event linked to treatment: abdominal pain	Injection site pain, fatigue, pyrexia, arthralgia, dizziness, headache, abdominal pain, vomiting, hemorrhage, hypotension, exacerbated dyspnea, erythema, skin ulcer, injection site edema/hypersensitivity, vasodilation, flatulence, ecchymosis, bone pain, increased cough, pneumonia, rhinitis, pruritus, rash, skin discoloration	NA
Gaudy et al	2006	ILT	NA	NA	0	No adverse effects from treatment occurred	NA
Dummer et al	2008	ILT*	NCI CTC v2.0	"Most mild to moderate adverse events"	Seven "serious" events (thrombocytopenia, pleural effusion, lymphocytopenia, anemia	Injection site pain, increase in tumor pain, chills, fatigue, fever, nausea, vomiting, constipation, stomach pain, headache, asthenia, lymphocytopenia/thrombocytopenia, diarrhea	NA
Hofmann et al	2008	ILT	NCI CTC v2.0	Grade 1, 16 events; grade 2, 12 events; grade 3, one event	One lymphopenia	Local swelling and erythema, fever, fatigue, rigors, headache, pain, increase in blood pressure, lymphocytopenia	Lymphopenia resolved in 14 days
Thompson et al	2008	ILT	NA		"No serious adverse events"	Mild to moderate injection site pain (n = 8), local inflammation (n = 4), pruritus (n = 3)	NA
Bedikian et al	2010	ILT	NCI CTC v2.0	Grade 1, 199 events; grade 2, 19 events; grade 3 to 4, zero events	0	Myalgia (n = 23), pyrexia (n = 22), arthralgia (n = 19), headache (n = 19), injection site pain (n = 43), injection site erythema (n = 28), rigors (n = 33), fatigue, nonspecific arthritis (n = 1)	NA

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Table A5. Toxicity Details (continued)

Study	Year	Local Therapy	Toxicity Grading Scale Listed	Details of Toxicity by Grade	Grade 3 or Higher or Severe Toxicity	Toxicities Reported	Toxicity Resolution
Weide et al	2010	ILT	CTC v3	Grade 1, < 70% of patients; grade 2, < 60% of patients	0	Inflammatory injection site reaction (swelling, erythema locally), necrosis, injection pain, fever 58%, fatigue 36%, nausea 34%, stomach pain (n = 4), myalgia (n = 4), headache (n = 4), itching exanthem (n = 3), dry oral mucosa (n = 2), pruritus (n = 2), hair loss (n = 1), diarrhea (n = 1), urticaria (n = 1), atopic dermatitis worsening (n = 1), single episode mild cardiac arrhythmia (n = 1), vitiligo-like depigmentation around treated metastases (n = 1)	NA
Unger et al	1992	TT	WHO	Grade 1 erythema, four of 24; grade 2 erythema, one of 24	0	Itching, slight erythema, scaling, dryness	NA
Unger et al	1993	TT	WHO	NA	0	Skin pruritus (two of 74), rash, dry skin, bleeding, and skin atrophy	NA
Terwogt et al	1999	TT	WHO	Grade 1, five; grade 2, 15; grade 3, one; unknown, one	One of 33 had "severe" skin reaction	22 of 33 adverse skin reactions including dryness, erythema, itch, pain, desquamation. Nausea in two patients.	NA
Smorenburg et al	2000	TT*	WHO	Local: grade 1, nine; grade 2, two; systemic: grade 1, three; grade 2, one	No grade 3 or 4 local or systemic events	Skin atrophy (20%), exfoliation (15%), rash (10%), pruritus (10%), pain (15%), dry skin (10%), telangiectasis (5%), nausea/vomiting (5%), anorexia (5%), fatigue (5%)	NA
Leonard et al	2001	TT*	NCI CTC 1986	Grade 1, three of 24; grade 2, 11 of 24; grade 3, four of 24; grade 4, four of 24	Eight of 24 had "significant" to "severe" local skin reaction	Dryness, erythema, desquamation, local pain, burning, itching. Rare ulcerating dermatitis.	NA
Eilender et al	2006	TT*	CTC v2.0	Total cohort (n = 27); grade 1 to 2, 10; grade 3 to 4, zero	0	Anemia, itching, burning, rash (most patients had no toxicity)	NA
Salazar et al	2011	TT*	CTCAE v3.0	"Primarily grade 1 to 2 neutropenia, anemia, grade 1 skin toxicity"	NA	NA	NA
Florin et al	2012	TT	NA	NA	0	Local inflammation, ulceration, erythema	
Adams et al	2012	TT*	CTCAE v 3.0	Local: grade 1, five of 10; grade 2, two of 10; systemic: grade 1, two; grade 2, two	No grade 3 or 4 local or systemic events	Local pain (n = 3), infection (n = 1), itching (n = 3), burning (n = 1), desquamation (n = 3), flu-like symptoms	NA
Plesnicar et al	1982	ILT + RT	NA	NA	NA	Marked erythema, ulceration, crusting, short flu-like syndrome	NA

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Table A5. Toxicity Details (continued)

Study	Year	Local Therapy	Toxicity Grading Scale Listed	Details of Toxicity by Grade	Grade 3 or Higher or Severe Toxicity	Toxicities Reported	Toxicity Resolution
Lai et al	2003	TT + RT	CTC v2.0, 1999	Grade 1, 11; grade 2, eight; grade 3, two	Two of seven had grade 3 acute radiation dermatitis	Nausea, anorexia, acute/chronic radiation dermatitis, fatigue	All grade 3 toxicity resolved 2 to 3 weeks post-radiotherapy
Green et al	2007	TT + ILT	Simply said "Grade 3"	NA	One patient had rigors	Erythema, discharge, mild influenza like symptoms, rigors (n = 1), local infections (n = 2), nausea/dyspepsia (n = 2)	Most symptoms resolved within the first "few weeks"
Li et al	2010	TT + PDT	NCI CTC v3.0, 2009	NA	Grade 3 occurred in 25% of patients (fatigue, pain requiring narcotics, dyspnea, cellulitis)	Rash (90%), pruritus (82%), pain (55%), fatigue (55%), anorexia (55%), nausea (36%), weight loss (36%), fever (18%), chills (9%), vomiting (9%), cellulitis (9%)	NA

Abbreviations: CALGB, Cancer and Leukemia Group B; CTC, Common Toxicity Criteria; CTCAE, Common Terminology Criteria for Adverse Events; DIC, disseminated intravascular coagulation; ECT, electrochemotherapy; ILT, intralesional therapy; LFT, liver function test; NA, not available; NCI, National Cancer Institute; NIH, National Institutes of Health; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy.

*Systemic therapy allowed.

†Toxicity grading scale from Overgaard J: Cancer 48:1116-1123, 1981.

‡Study split up by drug used for ILT injections.

§Study split by histology if toxicity information was extractable by histology.

Table A6. QOL Details

Study	Year	Local Therapy	QOL Scales Used	Results
Marty et al	2006	ECT	VAS	Patients treated with general anesthesia had lower pain scores than those with local anesthesia; 93% would be willing to undergo another treatment if indicated.
Campana et al	2012	ECT	Four-point pain scale	Pain scores improved from 1 week to 1 month post-ECT. Pain worsened with increased number of ECT treatments.
Kendler et al	2013	ECT	VAS and two custom QOL questions	Mean pain scores increased at time of treatment, but dropped below baseline value by 15 minutes post-treatment and remained low. QOL questions demonstrated improvement in all patients.
Leonard et al	2001	TT*	Rotterdam Symptom Checklist and a body image scale	Improved psychological distress from baseline and over placebo at last follow-up.
Lai et al	2003	TT + RT	Change in daily wound dressings and VAS	Treatment significantly reduced need for daily wound dressing changes and pain.

Abbreviations: ECT, electrochemotherapy; QOL, quality of life; RT, radiotherapy; TT, topical therapy; VAS, visual analogue scale (to assess pain).
*Systemic therapy allowed.

Table A7. Jadad Scale for Randomized Controlled Trials

		Jadad Scale[65]			
Study	Year	Randomization	Blinding	Withdrawal	Total
Sersa et al	2000	1	0	0	1
Byrne et al	2005	1	0	1	2
Gaudy et al	2006	1	0	1	2
Overgaard et al	1985	1	0	0	1
Cohen et al	1978	2	0	0	2
Nathanson et al	1979	2	0	1	3
Cascinelli et al	1993	2	2	1	5
Leonard et al	2001	1	1	1	3

Table A8. National Institutes of Health Level of Evidence Scale (all studies)

Study	Year	Level of Evidence[64]
Heller et al	1996	2
Sersa et al	2000	1B
Rodriguez-Cuevas et al	2001	2
Byrne et al	2005	1B
Gaudy et al	2006	1B
Marty et al	2006	2
Quaglino et al	2008	2
Matthiessen et al	2011	2
Benevento et al	2012	3B
Campana et al	2012	2
Kendler et al	2013	2
Sperduto et al	1991	2
Cairnduff et al	1994	2
Baas et al	1996	2
Kaplan et al	1998	2
Mang et al	1998	2
Overgaard et al	1985	1B
Menendez et al	2009	2
Cohen et al	1978	1B
Nathanson et al	1979	1B
Cascinelli et al	1993	1A
Stewart et al	1999	2
Hoeller et al	2001	2
Stopeck et al	2001	2
Radny et al	2003	2
Oratz et al	2003	2
Triozzi et al	2005	2
Gonzalez et al	2006	1B
Kimata et al	2006	2
Dummer et al	2008	2
Hofmann et al	2008	2
Thompson et al	2008	2
Bedikian et al	2010	2
Weide et al	2010	2
Unger et al	1992	2
Unger et al	1993	2
Terwogt et al	1999	2
Smorenburg et al	2000	2
Leonard et al	2001	1A
Eilender et al	2006	2
Salazar et al	2011	2
Florin et al	2012	2
Adams et al	2012	2
Plesnicar et al	1982	2
Lai et al	2003	2
Green et al	2007	2
Li et al	2010	2

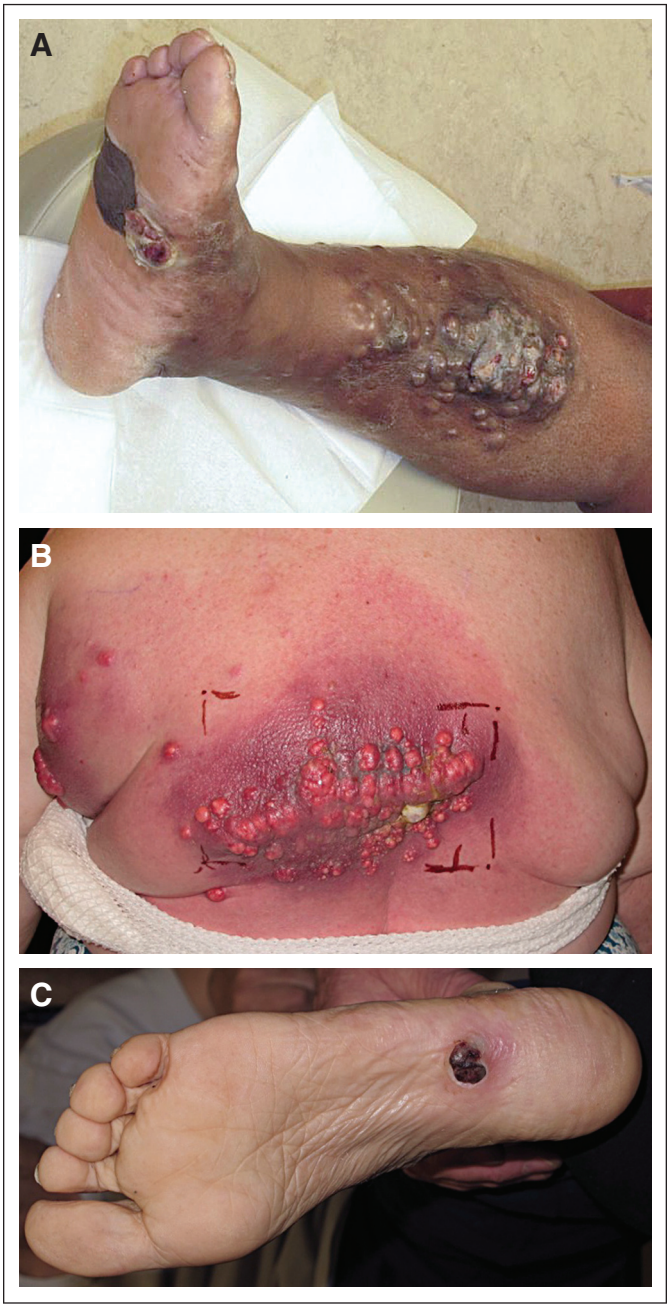

Fig A1. Examples of morbidity of cutaneous metastases. (A-C) Representative examples of cutaneous metastases from patients with melanoma.

Study name	Histology	Event rate	Lower limit	Upper limit	Total
Heller et al (b)	Adenocarcinoma of unknown primary	0.833	0.194	0.990	2/2
	Adenocarcinoma of unknown primary	0.833	0.194	0.990	2/2
Eilender et al (c)	Angiosarcoma	0.500	0.059	0.941	1/2
	Angiosarcoma	0.500	0.059	0.941	1/2
Eilender et al (a)	Breast	0.167	0.042	0.477	2/12
Adams et al	Breast	0.200	0.050	0.541	2/10
Unger et al	Breast	0.212	0.121	0.343	11/52
Smorenburg et al	Breast	0.222	0.086	0.465	4/18
Kendler et al (b)	Breast	0.241	0.120	0.427	7/29
Stewart et al (a)	Breast	0.250	0.063	0.623	2/8
Unger et al	Breast	0.292	0.146	0.498	7/24
Cairnduff et al	Breast	0.357	0.157	0.624	5/14
Gaudy et al	Breast	0.375	0.179	0.623	6/16
Leonard et al	Breast	0.421	0.226	0.644	8/19
Terwogt et al	Breast	0.433	0.271	0.612	13/30
Sperduto et al	Breast	0.650	0.426	0.823	13/20
Salazar et al	Breast	0.700	0.376	0.900	7/10
Lai et al	Breast	0.857	0.419	0.980	6/7
Baas et al	Breast	0.900	0.676	0.975	18/20
Campana et al	Breast	0.914	0.766	0.972	32/35
Benevento et al	Breast	0.923	0.866	0.957	131/142
Rodriguez-Cuevas et al (a)	Breast	0.967	0.634	0.998	14/14
Mang et al	Breast	0.994	0.915	1.000	86/86
	Breast	0.564	0.385	0.728	374/566
Eilender et al (d)	Kaposi's sarcoma	0.500	0.123	0.877	2/4
	Kaposi's sarcoma	0.500	0.123	0.877	2/4
Kendler et al (a)	Melanoma	0.010	0.001	0.138	0/50
Triozzi et al	Melanoma	0.033	0.002	0.366	0/14
Bedikian et al	Melanoma	0.059	0.036	0.095	15/255
Gonzalez et al	Melanoma	0.091	0.044	0.179	7/77
Stopeck et al	Melanoma	0.172	0.074	0.353	5/29
Dummer et al	Melanoma	0.240	0.112	0.442	6/25
Byrne et al	Melanoma	0.316	0.149	0.548	6/19
Stewart et al (b)	Melanoma	0.333	0.146	0.594	5/15
Eilender et al (b)	Melanoma	0.400	0.100	0.800	2/5
Hofmann et al	Melanoma	0.400	0.100	0.800	2/5
Thompson et al	Melanoma	0.423	0.252	0.615	11/26
Nathanson et al	Melanoma	0.455	0.265	0.659	10/22
Sersa et al	Melanoma	0.481	0.304	0.664	13/27
Heller et al (a)	Melanoma	0.500	0.225	0.775	5/10
Cascinelli et al	Melanoma	0.511	0.371	0.649	24/47
Green et al	Melanoma	0.517	0.444	0.589	92/178
Oratz et al	Melanoma	0.533	0.470	0.595	130/244
Gaudy et al	Melanoma	0.583	0.383	0.759	14/24
Menendez et al	Melanoma	0.693	0.590	0.780	61/88
Hoeller et al	Melanoma	0.714	0.327	0.928	5/7
Byrne et al	Melanoma	0.736	0.602	0.837	39/53
Plesnicar et al	Melanoma	0.789	0.554	0.919	15/19
Weide et al	Melanoma	0.794	0.766	0.819	710/894
Kimata et al	Melanoma	0.800	0.309	0.973	4/5
Cohen (a)	Melanoma	0.839	0.781	0.884	167/199
Cohen (b)	Melanoma	0.847	0.814	0.874	480/567
Quaglino et al	Melanoma	0.927	0.886	0.954	216/233
Li et al	Melanoma	0.958	0.575	0.997	11/11
Rodriguez-Cuevas et al (b)	Melanoma	0.964	0.616	0.998	13/13
Overgaard et al	Melanoma	0.969	0.650	0.998	15/15
Radny et al	Melanoma	0.970	0.939	0.986	230/237
Florin et al	Melanoma	0.978	0.858	0.997	44/45
	Melanoma	0.585	0.467	0.693	2,357/3,458
Rodriguez-Cuevas et al (c)	SCC (upper aerodigestive tract)	0.833	0.194	0.990	2/2
	SCC (upper aerodigestive tract)	0.833	0.194	0.990	2/2
Tumor type variation ($P = .003$)					

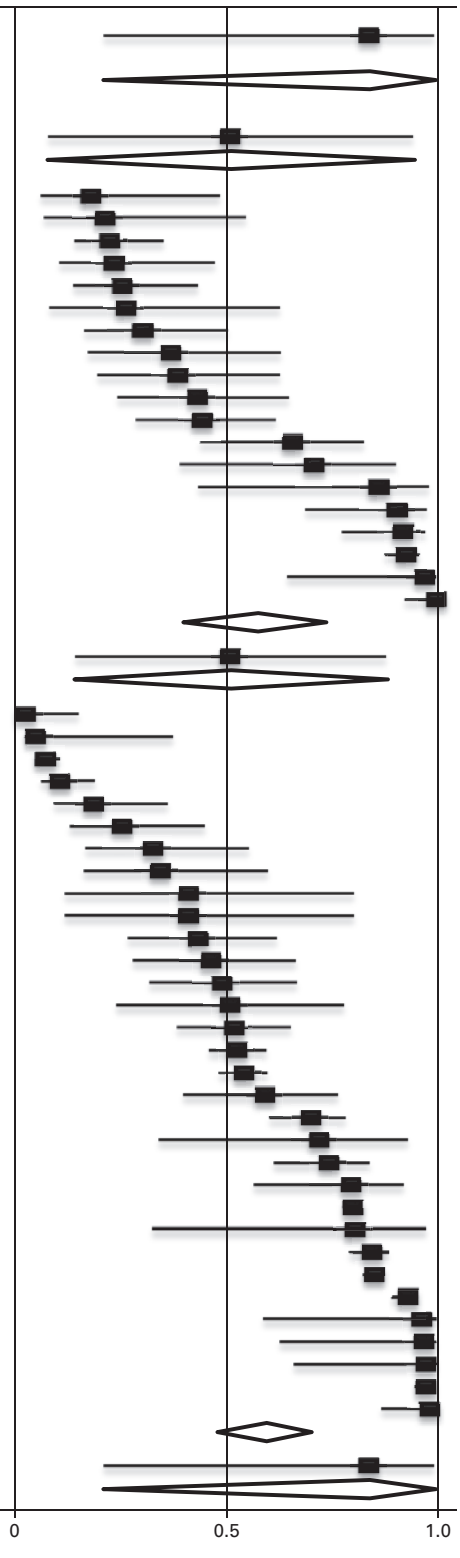

Fig A2. Meta-analysis of objective response by histology. (a-d) indicate unique histology from the same study. NOTE. Total column indicates No. of objective responses/No. of cutaneous metastases. SCC, squamous cell cancer.

Study name	Treatment modality	Event rate	Lower limit	Upper limit	Total
Byrne et al	ECT	0.028	0.002	0.322	0/17
Gaudy et al	ECT	0.083	0.021	0.279	2/24
Heller et al	ECT	0.125	0.007	0.734	0/3
Campana et al	ECT	0.143	0.061	0.300	5/35
Quaglino et al	ECT	0.991	0.871	0.999	54/54
	ECT	0.245	0.041	0.714	61/133
Byrne et al	ILT	0.025	0.002	0.298	0/19
Gonzalez et al	ILT	0.029	0.002	0.336	0/16
Bedikian et al	ILT	0.600	0.348	0.808	9/15
	ILT	0.116	0.006	0.748	9/50
Mang et al	PDT	0.006	0.000	0.085	0/86
Cairnduff et al	PDT	0.083	0.005	0.622	0/5
	PDT	0.022	0.001	0.248	0/91
Overgaard et al	RT	0.133	0.034	0.405	2/15
	RT	0.133	0.034	0.405	2/15
Florin et al	TT	0.011	0.001	0.154	0/44
	TT	0.011	0.001	0.154	0/44
	Overall $P = .27$	0.092	0.037	0.212	72/333

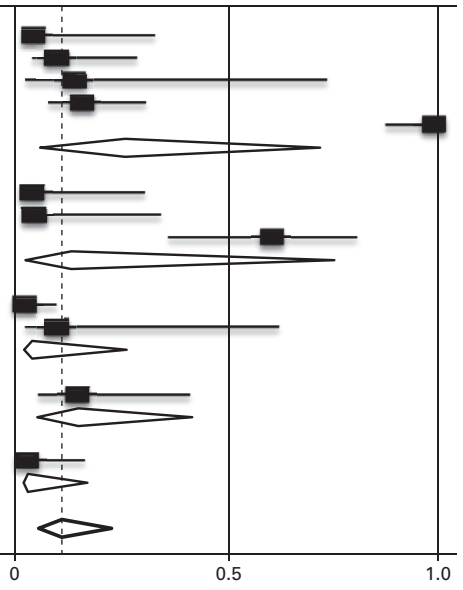

Fig A3. Meta-analysis of recurrence rates by skin-directed therapy. NOTE. Total column indicates No. of recurrences/No. of cutaneous metastases. ECT, electrochemotherapy; ILT, intralesional therapy; PDT, photodynamic therapy; RT, radiotherapy; TT, topical therapy.

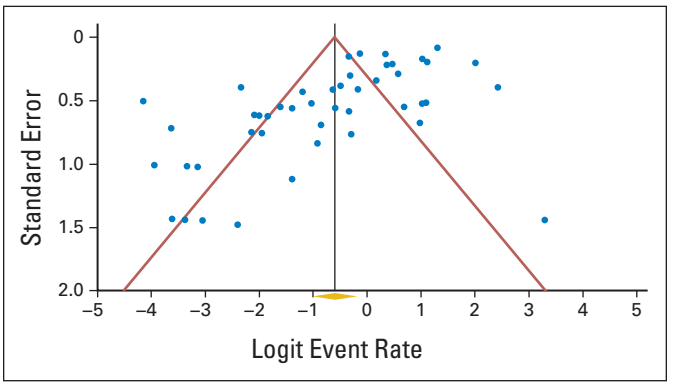

Fig A4. Funnel plot of standard error by logit event rate for complete response. Egger's regression $P < .001$.

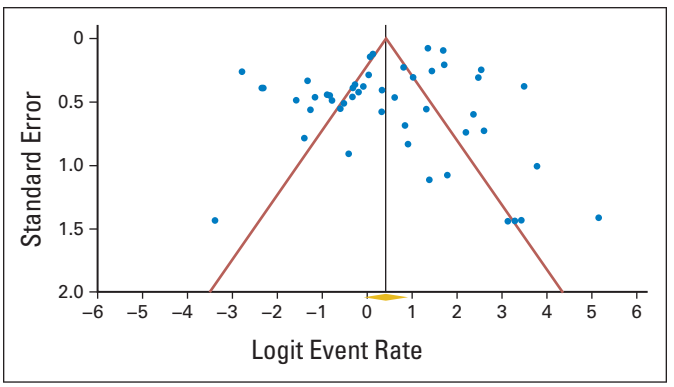

Fig A5. Funnel plot of standard error by logit event rate for objective response. Egger's regression $P = .06$.