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Systematic or Meta-analysis Studies

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

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ABSTRACT

Background and purpose: Both stereotactic radiotherapy (SRT) and immune- or targeted therapy play an increasingly important role in personalized treatment of metastatic disease. Concurrent application of both therapies is rapidly expanding in daily clinical practice. In this systematic review we summarize severe toxicity observed after concurrent treatment.

Material and methods: PubMed and EMBASE databases were searched for English literature published up to April 2016 using keywords "radiosurgery", "local ablative therapy", "gamma knife" and "stereotactic", combined with "bevacizumab", "cetuximab", "crizotinib", "erlotinib", "gefitinib", "ipilimumab", "lapatinib", "sorafenib", "sunitinib", "trastuzumab", "vemurafenib", "PLX4032", "panitumumab", "nivolumab", "pembrolizumab", "alectinib", "ceritinib", "dabrafenib", "trametinib", "BRAF", "TKI", "MEK", "PD1", "EGFR", "CTLA-4" or "ALK". Studies performing SRT during or within 30 days of targeted/immunotherapy, reporting severe ($\geqslant$Grade 3) toxicity were included.

Results: Concurrent treatment is mostly well tolerated in cranial SRT, but high rates of severe toxicity were observed for the combination with BRAF-inhibitors. The relatively scarce literature on extracranial SRT shows a potential risk of increased toxicity when SRT is combined with EGFR-targeting tyrosine kinase inhibitors and bevacizumab, which was not observed for cranial SRT.

Conclusions: This review gives a best-possible overview of current knowledge and its limitations and underlines the need for a timely generation of stronger evidence in this rapidly expanding field.

Introduction

The management of cancer patients with locally recurrent or (oligo)metastatic disease has changed fundamentally since the introduction of immunotherapy and personalized targeted therapy. In parallel, stereotactic radiotherapy (SRT) has become broadly available and is increasingly used in the same cancer patient population. An improved understanding of the biological behaviour of metastatic disease, longer survival and the availability of these new treatment options has warranted a reconsideration of previous dogmas related to the combination of targeted systemic and local therapies, up to a point where a combination of both is now recommended in multidisciplinary international practice guidelines (NCCN, IASLC) [1,2].

SRT differs substantially from conventionally fractionated radiotherapy, which traditionally has been used in the metastatic setting: high radiation doses aim at long term local tumour control rather than short-term palliation [3]. Interactions between conventionally fractionated radiotherapy and targeted agents are reasonably well understood and toxicity data are available in the literature [4]. However, it is uncertain whether these observations can be extrapolated to SRT, which differs from conventionally fractionated radiotherapy in a physics, biological and technological perspective. With SRT, high radiation doses have been shown to cause direct vascular damage and endothelial apoptosis, thereby increasing tumour cell-destruction [5,6]. Furthermore, SRT might stimulate the antitumour immune response, that will act both

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locally within the irradiated volume as well as systemically and could enhance the effectivity of immunotherapies [7–9]. Although the sparing of healthy tissue from higher irradiation doses makes radiotherapy less toxic, the spread of low irradiation doses over large volumes of parallel organs such as the lung may potentially increase toxicity [10]. Consequently, differences in radiobiology [11] might result in unexpected interactions and toxicity profiles within a multimodality treatment strategy. This systematic review aimed to summarize all currently available published data about toxicity of concurrent SRT and targeted therapy or immunotherapy.

Material and methods

We performed a systematic literature search according to the 'PRISMA' guideline [12]. PubMed and EMBASE databases were searched with the MeSH and free text search terms "radiosurgery", "local ablative therapy", "gamma knife" and "stereotactic", combined with "bevacizumab", "cetuximab", "crizotinib", "erlotinib", "gefitinib", "ipilimumab", "lapatinib", "sorafenib", "sunitinib", "trastuzumab", "vemurafenib", "PLX4032" "panitumumab", "nivolumab", "pembrolizumab", "alectinib", "ceritinib", "dabrafenib", "trametinib", "BRAF", "TKI", "MEK", "PD1" "EGFR", "CTLA-4" or "ALK". The targeted agents were selected based on approval for use in solid tumour types that are also regularly treated with SRT. The search for publications was limited to the English language and original articles. No limitation was placed on publication year; studies published up to the end of April 2016 were reviewed. Only original articles were included. Conference abstracts, reviews, book chapters, commentaries, editorials and articles that were not peer-reviewed were excluded. References from included studies were reviewed and cross-referenced to ensure completeness.

SRT was defined by fraction doses $\geqslant$5 Gy and $\leqslant$8 fractions. Targeted therapy had to be given concurrently to SRT, or initiated within 30 days before or after radiation. Studies treating benign diseases or patients younger than 18 years old, not (clearly) describing toxicity or timing of SRT in relation to targeted therapy were excluded. Toxicity had to be either graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), or properly described. When toxicity was not graded according to the CTCAE, the authors rated the toxicity accordingly.

Two authors (S.K. and C.F.) performed the study selection independently. Disagreements were resolved by consensus with the senior author (M.G.). Titles and abstracts were used to screen for initial study inclusion. Full-text review was used when the abstract provided insufficient data to determine whether the study met inclusion or exclusion criteria. Two authors (S.K. and C.F.) performed all data abstraction. The following data was extracted: year of publication of the study, study type, patient and tumour characteristics, radiation dose and fractionation, type and dosage of targeted therapy used, timing of the concurrent targeted therapy and radiotherapy and toxicity. Only Grade 3 or higher toxicities were included for analysis.

Results

Included studies and overview

Our literature search identified 1038 references (Fig. 1). After adjusting for duplicates 843 unique citations remained and following title and abstract review, 102 relevant articles underwent full text review. Of these, 53 did not meet the inclusion criteria, resulting in 49 remaining articles that were included into this systematic review (Tables 1a and b). These included 13 (321 patients) prospective studies, 27 (653 patients) retrospective studies and 9 (16 patients) case reports. No articles reporting toxicity of SRT with concurrent lapatinib, panitumumab, alectinib, ceritinib and pembrolizumab were found. The number of patients per study ranged from 1 to 106 patients, with a median of 15 patients (Table 2). Whereas SRT for intra-cranial lesions was reported in 34 studies, SRT for extra-cranial sites was only reported in 19 studies (Fig. 2).

For targeted agents combined with cranial SRT (n = 644), grade 3, grade 4 and grade 5 toxicity was observed in 74 (11%), 14 (2%) and 1 patient(s), respectively (Fig. 3a). Less than half (5.4% Gr3; 0.6% Gr4; 0% Gr5) of these adverse events were considered directly related to the SRT (Table 2). For extra-cranial SRT (n = 524), severe toxicity was reported as grade 3 in 73 (14%), grade 4 in 8 (2%) and grade 5 in 3 patients (0.6%) (Fig. 3b). Approximately half of these toxicities could be related to the SRT or the concurrent therapy (7.6% Gr3; 0.8% Gr4; 0.6% Gr5) (Table 2). Overall, SRT-induced severe toxicity was lower for cranial compared to extra-cranial SRT (6% vs. 9%). The remaining events were attributed to the targeted therapy alone (Table 2, Fig. 4).

Toxicity of concurrent SRT and antibody therapy

Anti-VEGF (bevacizumab)

SRT was combined with bevacizumab in 4 prospective [13–16], 7 retrospective studies [17–23] and 1 case report [24]. All but one reported on cranial SRT of (recurrent) glioblastoma (GBM) or brain metastases (Table 1b). Radiation was performed with a median dose of 12.5 to 24 Gy in 1 fraction or 20 to 50 Gy in 3–6 fractions. The median follow-up ranged from 4 to 42 months. In total, 47 severe toxicity events ($\geqslant$Grade 3) were reported in 206 patients (Table 2, Fig. 4).

For cranial SRT, grade 3/4 toxicity outside the radiation field was observed in 16% of patients and consisted mainly of haematological disorders (Table 2). No grade 5 toxicity was reported. Severe local toxicity within the irradiated volume was observed in 12 out of 192 patients (6%) (Table 2b). Of these, 2 were grade 4 (wound-healing disorder, surgical wound infection). Grade 3 toxicity within the irradiated volume consisted of radionecrosis (n = 1), headache (n = 1), worsening of neurological symptoms (n = 1), change in memory (n = 1), wound dehiscence (n = 1), CNS haemorrhage (n = 1), dysphasia (n = 1) and seizures (n = 2). Cuneo et al. compared SRT alone to SRT with bevacizumab and found that toxicity rates did not differ significantly [20]. One study reported a decreased risk of radionecrosis and cerebral oedema after SRT combined with bevacizumab [16].

For extra-cranial SRT, only the study of Barney et al. reported 14 patients treated with bevacizumab within one month after abdominal SRT [17]. SRT was performed with a median dose of 50 Gy in 1 to 5 fractions. One grade 4 gastric perforation was observed in a patient that started bevacizumab two weeks after SRT, and one grade 3 gastric ulcer in a patient that received concurrent therapy [25].

In summary, the additional risk of concurrent cranial SRT and bevacizumab appears to be small or non-existing in terms of neurological toxicity, and could possibly even be protective to the development of radionecrosis. Data on the combination of bevacizumab and SRT at extra-cranial locations is scarce but indicates that the use of concurrent abdominal SRT and bevacizumab should be practised with caution.

Anti-EGF-R (cetuximab)

Three prospective [26–28] and 3 retrospective trials [29–31] were identified (n = 224 patients, Table 2). All evaluated recurrent head-and-neck cancer (HNC) and initiated cetuximab 1 week before SRT. The median SRT dose was 36 or 40 Gy in 5 or 6 frac-

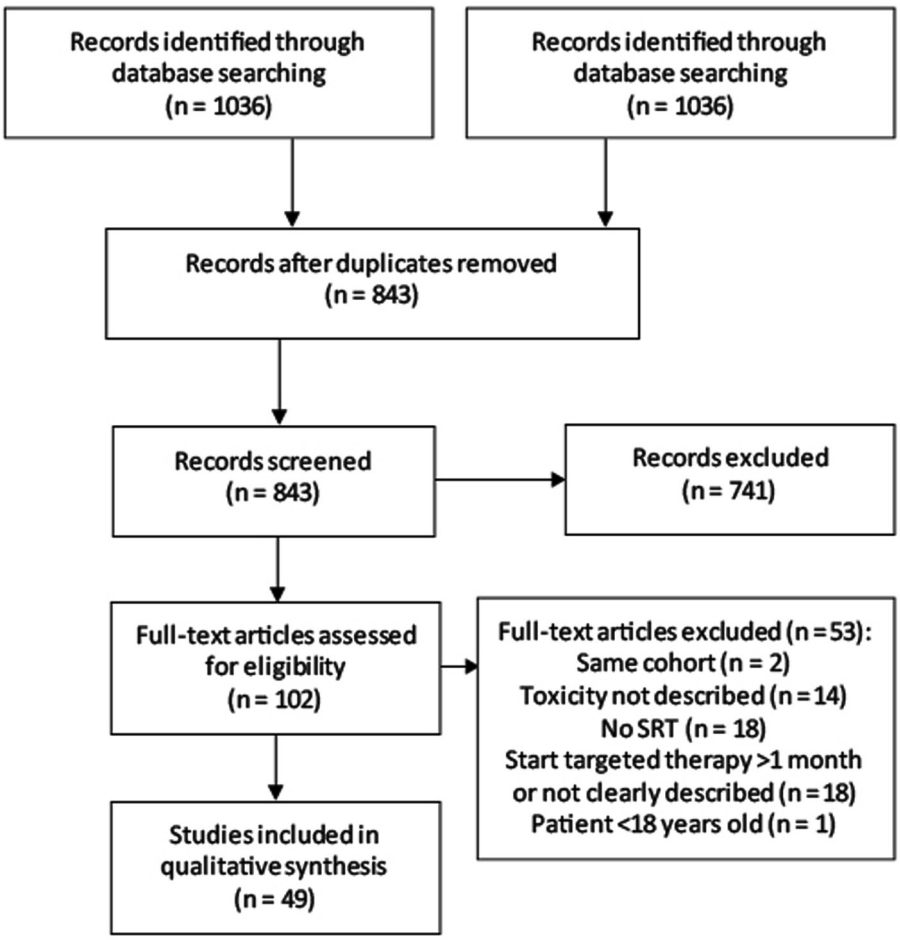

Fig. 1. Search flow diagram.

tions. Median follow-up ranged from 6 to 25.6 months. Overall, 32 severe toxicities were observed in 172 patients (19%), of which 31 were grade 3 and 1 grade 5 (Table 2, Fig. 1a). The most commonly observed toxicity within the irradiated volume was dermatitis ($n = 6$), mucositis ($n = 7$) or dysphagia ($n = 8$). The single grade 5 toxicity represented a patient with severe malnutrition and fatal bleeding [27]. The retrospective study by Vargo et al. observed a significant increase in severe acute toxicity of a concurrent therapy compared to SRT alone (13 vs. 10%, $p = 0.008$), whereas severe late toxicity was not significantly more prevalent [28]. A potentially increased grade 3 toxicity of combined SRT and cetuximab compared to SRT alone was also reported by Comet et al. (3 of 15 vs. 1 of 25 patients); no statistical analysis was performed in this small number of patients [26].

In summary, cetuximab has been combined with SRT only for treatment of recurrent HNC in previously irradiated patients. There appears to be considerable risk of severe acute toxicity, but hypofractionated reirradiation of the head and neck alone is associated with a high risk of acute and late toxicity as well; consequently, it is not clear to which extent concurrent cetuximab adds to the toxicity.

Anti-Her2 (trastuzumab)

Only one case report has been published [32]. This study reported on 7 Her2 + breast cancer patients that received stereotactic radiosurgery (SRS) of 22 cerebral metastases, with concurrent trastuzumab therapy. Trastuzumab was initiated median 8.5 days after SRT, with a large range of 3 to 449 days. SRS was performed with single fraction doses of 18, 20 or 24 Gy. Acute grade 4 cerebral oedema was observed in 1 patient (14%). No late toxicity was observed.

In summary, the very limited available data does not indicate increased toxicity of cranial SRT combined with trastuzumab. Data on the combination of trastuzumab and extra-cranial SRT is lacking.

Toxicity of concurrent SRT and immune checkpoint inhibition

Anti-CTLA-4 (ipilimumab)

Six retrospective studies [33–38] and 2 case reports [39,40] were identified (Table 2). All retrospective analyses examined SRT concurrent to ipilimumab in melanoma brain metastases. The median SRT dose ranged from 14 to 60 Gy in 1–5 fractions and median follow-up ranged between 7.3 and 33.1 months. Severe toxicities were mainly ipilimumab-induced, and ipilimumab combined with SRT did not increase toxicity compared to ipilimumab alone (Table 2) [36]. Kiess et al. observed 2 grade 3 seizures and 2 grade 3 CNS haemorrhages (13%) that could be attributed to SRT alone or the concurrent treatment [33] and there was a trend towards increased CNS toxicity in the concurrent therapy group. In addition, studies of Silk et al., Mathew et al. and Patel et al. did not find increased toxicity after combined treatment [34,35,37]. Symptomatic radiation necrosis after the combined therapy was observed in the study of Patel et al., but not more frequently than after SRT alone [35].

Table 1a
Included articles with concurrent SRT and tyrosine kinase inhibitor treatment.

Study	Study year	Study type	*N* (patients/ lesions)	Dose (Gy) (median/ fractions)	Targeted drug	Start of targeted drug	Primary tumor	Treated site	Treatment timing	Follow-up (median months)	Toxicity (⩾3)	Infield Toxicity (⩾3)
Staehler et al. [44]	2010	Restrospective	106 (106)	20/1	Sorafenib 400 mg p.o/1 d (n = 45); Sunitinib 50 mg p.o./1 d 4 w in 6 w cycle (n = 61)	Concurrent	RCC	Brain; Spine	Advanced metastatic	14.7	Y	Y
Brade et al. [45]	2016	Phase 1 trial	16 (16)	33, 51/6	Sorafenib 200 mg/400 mg p.o./1 d	Concurrent, start 7 d before SRT	HCC	Liver	Primary treatment	11	Y	Y
Straka et al. [46]	2013	Case report	1 (1)	60/5	Sunitinib, dosage NR	14 m before SRT, paused during SRT	RCC	Adrenal	Oligoprogression	8	N	N
Ahluwalia et al. [43]	2015	Phase 2 trial	14 (25)	SRS dose NR	Sunitinib 37.5 mg or 50 mg p.o./ 1 d, 4 w in 6 w cycle	Start up to 1 m after SRT	Lung cancer (n=6); Breast cancer (n=3), Melanoma (n=2); Other (n=3)	Brain	Oligoprogression	11.7	Y	N
Wang et al. [51]	2014	Prospective	14 (14)	45, 60/3	Gefitinib 250 mg p.o./1 d	Concurrent, start 7 d before SRT	NSCLC	Lung	Advanced metastatic	15.5	Y	Y
Schwer et al. [49]	2008	Phase 1 trial	15 (15)	range 18–36/3	Gefitinib 250 mg p.o./1 d	Concurrent, start 7 d before SRT	Glioma	Brain	Local recurrence	7	N	N
Kim et al. [48]	2015	Restrospective	18 (31)	23/1	Gefitinib 250 mg p.o./1 d; Erlotinib 150 mg p.o./1 d	Concurrent	NSCLC	Brain	Advanced metastatic	31.9	N	N
Iyengar et al. [47]	2014	Phase 2 trial	24 (52)	range 19–40/ 1–5	Erlotinib 150 mg p.o./1 d	Concurrent, start 1–3 w before SRT	NSCLC	Lung; Liver; Kidney; Bone; Adrenal; Mediastinum; Lymph node	Oligometastatic disease	11.6	Y	Y
Gan et al. [52]	2014	Restrospective	14 (29)	range 12–54/ 1–3	Crizotinib, dosage NR	Concurrent, paused during SRT	NSCLC	extraCNS (lung, liver, other locations NR)	Oligoprogression	11.5	N	N
Weickhardt et al. [50]	2012	Retrospective	25 (NR)	SRT or SRS dose NR	Crizotinib 250 mg p.o./2xd (n = 15); Erlotinib 150 mg p.o./1d (n = 10)	Concurrent, paused during SRT	NSCLC	Brain; Lung; Lymph node; Bone; Liver; Adrenal	Oligoprogression	20	N	N
Ahmed et al. [54]	2015	Retrospective	24 (80)	21/1	Vemurafenib 960 mg p.o./2xd	Median 5.2 m (0.4–17.1 m) before SRT, paused 2–3 days before/ after SRT	Melanoma	Brain	Oligometastatic disease	5.1	Y	Y
Peuvrel et al. [60]	2013	Case report	1 (2)	20/1	Vemurafenib 960 mg p.o./2xd	3 months before SRT, concurrent	Melanoma	Brain	Oligoprogression	NR	Y	Y
Narayana et al. [57]	2013	Retrospective	6 (14)	20/1	Vemurafenib 960 mg p.o./2xd	Before, concurrent or after SRT median 8.7 w (range 2.6–113.6 w)	Melanoma	Brain	Advanced metastatic	12.2	N	N
Ly et al. [57]	2015	Restrospective	17 (96)	20/1	Vemurafenib 720 mg (n = 4) or 960 mg (n = 3) p.o./2xd (n = 4); Dabrafenib 150 mg p.o./2xd (n = 9); unknown BRAF-Inhibitor (n = 1)	Before or after SRT, paused during SRT median 7 days, range 1–20 days	Melanoma	Brain	Advanced metastatic	10.5	NR	NR
Liebner et al. [59]	2014	Case report	2 (4)	22, 24, 27/1 or 30/5	Vemurafenib 960 mg p.o./2xd	1–3 m before SRT, paused during SRT	Melanoma	Brain	Advanced metastatic	NR	Y	Y
Stefan et al. [61]	2016	Case report	1 (1)	10/1	Vemurafenib 960 mg p.o./2xd	Concurrent, 1 m before SRT	Melanoma	Spine	Advanced metastatic	NR	N	N
Gaudy et al. [55]	2014	Retrospective	24 (209)	20, 28/1	Vemorafenib (n = 20); Dabrafenib (n = 4), dosage NR	Concurrent (n = 20) 2.5 t1/2 after SRT (n = 4)	Melanoma	Brain	Advanced metastatic	4.7	Y	Y

Table 1a (*continued*)

Study	Study year	Study type	*N* (patients/ lesions)	Dose (Gy) (median/ fractions)	Targeted drug	Start of targeted drug	Primary tumor	Treated site	Treatment timing	Follow-up (median months)	Toxicity (⩾3)	Infield Toxicity (⩾3)
Wolf et al. [53]	2016	Prospective	31 (NR)	18/1	Dabrafenib; Vemurafenib; Dabrafenib and Trametinib, dosage NR	Concurrent (n = 6); before and after (n = 12); after (n = 12) > 1 months after SRT; before SRT (n = 1)	Melanoma	Brain	Advanced metastatic	NR	NR	NR
Hecht et al. [4]	2015	Retrospective	19 (NR)	SRS dose NR	Vemurafenib; Dabrafenib, dosage NR	Concurrent	Melanoma	Brain (n = 18), Body (n = 1)	Advanced metastatic	6.6	N	N
Patel et al. [58]	2016	Retrospective	4 (8)	21/1	Dabrafenib 150 mg p.o./2xd and Trametinib 2 mg p.o./1 d	Concurrent (n = 3), paused 2–3 days before/ after SRT, start 0.7 m after SRT (n = 1)	Melanoma	Brain	Advanced metastatic	10.6	N	N

Two case reports of SRT concurrent with ipilimumab in liver metastases from NSCLC and melanoma did not observe any significant toxicity [39,40].

In summary, the available studies are small but suggest that concurrent cranial SRT with ipilimumab is safe. There is very limited data on the use ipilimumab concurrent with extra-cranial SRT.

Anti-PD-1/PD-L1 (nivolumab, pembrolizumab)

Our search did not find studies on concurrent pembrolizumab and SRT. For nivolumab, only 1 case report of SRT for NSCLC brain metastases and 1 retrospective study of SRT for melanoma brain metastases was identified [41,42]. The case report by Alomari et al. observed a grade 4 cerebral oedema in one patient receiving concurrent therapy [41]. Ahmed et al. reported two events of grade 3 cerebral oedema in 20 patients treated with SRT and nivolumab for melanoma brain metastases (Table 2) [42].

In summary, the data on combined SRT and nivolumab is insufficient for conclusions, both for cranial and extra-cranial SRT. Data about the combination of pembrolizumab with SRT is not available.

Toxicity of concurrent SRT and tyrosine kinase inhibitors (TKIs)

Multi receptor tyrosine kinase inhibitors (sorafenib, sunitinib)

Two studies examined SRT of cerebral metastases from several tumour types [43,44]. In the retrospective study of Staehler et al. [44] where 51 patients received concurrent cranial SRT for cerebral metastases with sorafenib or sunitinib, no radiation necrosis was observed, but 1 patient developed a fatal cerebral bleeding 3 months after SRT concurrent with sunitinib. The prospective phase 2 trial of Ahluwalia et al. with concurrent sunitinib and SRT for cerebral metastases reported 12 severe toxicities in 8 out of 14 patients (57%), which were all extra-cranial and not likely caused by the radiation therapy (Table 2) [43].

We found 2 studies examining concurrent extra-cranial SRT with sorafenib [44,45] and 3 with sunitinib [43,44,46]. These studies were highly diverse in study type, tumour type and location of SRT. Three studies examined concurrent therapy with SRT in the abdomen: Brade et al. evaluated SRT of intrahepatic HCC, Straka et al. SRT of adrenal metastases in RCC and Staehler et al. SRT of spinal metastases in RCC [44–46]. Staehler et al. observed grade 3 toxicity in 23% of a total of 106 patients (n = 51 cranial and n = 55 extra-cranial), which were all attributed to the TKI therapy and not to concurrent SRT (Table 2) [44]. Brade et al. observed severe toxicity that was potentially caused by the concurrent SRT of HCC. [45] Grade 3 toxicity was observed in 9 of 16 patients (56%); SRT-induced toxicity included liver enzyme changes (n = 2) and lower GI haemorrhage (n = 1). Two patients developed grade 4 toxicity (13%), consisting of liver failure and small bowel obstruction. One patient died after an upper GI haemorrhage. Sorafenib had to be discontinued in 4 patients and 13 out of 16 patients required a dose modification. Straka et al. found no toxicity after treatment of one patient with sunitinib combined with SRT of an adrenal metastases of RCC [46].

In summary, cranial SRT combined with sorafenib of sunitinib appears to be safe but one grade 5 toxicity has been observed for sunitinib. For extra-cranial SRT, liver SRT combined with sorafenib is associated with a high risk of severe toxicity, which has not been observed for sorafenib and SRT in other extra-cranial locations. No radiation induced toxicity has been observed after sunitinib and extra-cranial SRT.

EGF-R-inhibitors (gefitinib, erlotinib, lapatinib)

Five studies (n = 81 patients) examining concurrent gefitinib or erlotinib and SRT were identified (Table 1a) [16,47–50]. These studies were diverse in study type and location of SRT, but mainly

Table 1b
Included articles with concurrent SRT and antibody treatment.

Study	Study year	Study type	*N* (patients/ lesions)	Median dose (Gy)/fractions	Targeted therapy	Start of targeted therapy	Primary tumor	Treated site	Treatment timing	Follow-up (median months)	Toxicity (⩾3)	Infield Toxicity (⩾3)
Cuneo et al. [20]	2012	Retrospective	42 (42)	15 (12.5–25)/ 1–5	Bevacizumab, dosage NR	Concurrent or after SRT	Glioma	Brain	Local recurrence	7	Y	NR
Gutin et al. [14]	2009	Prospective pilot study	25 (25)	30/5	Bevacizumab, 10 mg/ kg i.v./2 w	Concurrent	Glioma	Brain	Local recurrence	6.6	Y	Y
Wang et al. [16]	2014	Prospective pilot study	8 (8)	30/1–5	Bevacizumab, 5 mg/ kg i.v./2 w	Start 3–10 d (median 5 d) after SRT	CRC; NSCLC; Maxillary gland; Esophagus; Gastric	Brain	Oligometastatic disease	5	N	N
Yomo et al. [23]	2015	Retrospective	5 (9)	18/1	Bevacizumab, 7.5–10 mg/kg i.v./3-4 w	Start 1 d after SRT	NSCLC, CRC	Brain	Oligoprogression	4.5	Y	N
Minniti et al. [22]	2015	Retrospective	26 (26)	25/5	Bevacizumab, 10 mg/ kg iv./2 w	Concurrent	Glioma	Brain	Local recurrence	12	Y	Y
Omuro et al. [15]	2014	Phase 2 trial	40 (40)	36/6	Bevacizumab, 10 mg/ kg i.v. and Temozolamide 75 mg/m2 p.o.	Concurrent	Glioma	Brain	Primary treatment	42	Y	Y
Cabrera et al. [13]	2013	Prospective pilot study	15 (15)	24/1, 18/1, 25/5	Bevacizumab, 10 mg/ kg i.v./2 w	Concurrent	Glioma	Brain	Local recurrence	30	Y	Y
Clark et al. [18]	2014	Retrospective	21 (21)	30/5	Bevacizumab, 10 mg/ kg i.v.	Concurrent	Glioma	Brain	Local recurrence	8.5	Y	Y
Hasan et al. [21]	2015	Retrospective	9 (9)	25/3–5	Bevacizumab, dosage NR	Before or after SRT	Glioma	Brain	Local recurrence	5.3	N	N
Conde et al. [19]	2015	Retrospective	9 (9)	30/5	Bevacizumab, 10 mg/ kg i.v./2 w	Concurrent	Glioma	Brain	Local recurrence	38	NR	NR
Cabrera et al. [24]	2012	Case report	1 (1)	18/1	Bevacizumab, 10 mg/ kg i.v./2 w	Concurrent	Glioma	Brain	Local recurrence	4	N	N
Barney et al. [17]	2013	Retrospective	14 (NR)	50/1–5	Bevacizumab 5 mg or 10 mg/kg/2 w, or 15 mg/kg/3 w	Median 3.3 m, (range 0.0–4 m) after SRT	HCC; CRC; Pancreas; Melanoma; RCC	Lymph node; Liver; Pancreas	Advanced metastatic	15.4	Y	Y
Carlson et al. [32]	2014	Case report	7 (22)	18/1, 20/1, 24/1	Trastuzumab, dosage NR	Median 8.5d (range 3–449 d) after SRT	Her2 + breast cancer	Brain	Local recurrence	NR	Y	Y
Vargo et al. [28]	2015	Phase 2 trial	48 (48)	40/5	Cetuximab 400 mg/ m2 i.v., after that 250 mg/m2/1 w	Concurrent, start 7 d before SRT	SCCHN	Head-and-neck	Local recurrence	18	Y	Y
Lartigau et al. [27]	2013	Phase 2 trial	56 (56)	36/6	Cetuximab 400 mg/ m2 i.v., after that 250 mg/m2/1 w	Concurrent, start 7 d before SRT	SCCHN	Head-and-neck	Local recurrence	11.4	Y	Y
Vargo et al. [31]	2014	Retrospective	72 (72)	40/5	Cetuximab 400 mg/ m2 i.v., after that 250 mg/m2/1 w	Concurrent, start 7 d before SRT	HNC	Head-and-neck	Local recurrence	6	Y	NR
Comet et al. [26]	2011	Prospective pilot study	15 (15)	36/5	Cetuximab 400 mg/ m2 i.v., after that 250 mg/m2/1 w	Concurrent, start 7 d before SRT	HNC	Head-and-neck	Local recurrence	25.6	Y	Y
Heron et al. [29]	2011	Retrospective	35 (35)	40/5	Cetuximab 400 mg/ m2 i.v., after that 250 mg/m2/1 w	Concurrent, start 7 d before SRT	SCCHN	Head-and-neck	Local recurrence	15.9	Y	Y
Quan et al. [30]	2016	Retrospective	18 (18)	40/5	Cetuximab 400 mg/ m2 i.v., after that 250 mg/m2/1 w	Concurrent, start 7 d before SRT	SCCHN	Head-and-neck	Local recurrence	25.6	Y	Y
Kiess et al. [33]	2015	Retrospective	15 (NR)	21/1	Ipilimumab 3 mg or 10 mg/kg/3 w	Concurrent	Melanoma	Brain	Advanced metastatic	22	Y	Y

Table 1b (*continued*)

Study	Study year	Study type	*N* (patients/ lesions)	Median dose (Gy)/fractions	Targeted therapy	Start of targeted therapy	Primary tumor	Treated site	Treatment timing	Follow-up (median months)	Toxicity (⩾3)	Infield Toxicity (⩾3)
Golden et al. [39]	2013	Case report	1 (1)	60/5	Ipilimumab, 3 mg/kg i.v./3 w	Start 1 d after SRT	NSCLC	Liver	Oligoprogression	12	N	N
Tazi et al. [38]	2015	Retrospective	10 (59)	SRS, dose NR	Ipilimumab, dosage NR	Concurrent	Melanoma	Brain	Advanced metastatic	33.1	Y	N
Silk et al. [37]	1013	Retrospective	5 (NR)	Range 14–24/ 1–5	Ipilimumab, 3 mg/kg i.v./3 w	Concurrent	Melanoma	Brain	Advanced metastatic	19.9	NR	NR
Mathew et al. [34]	2013	Retrospective	25 (NR)	20/1	Ipilimumab, 3 mg/kg or 10 mg/kg i.v./3 w	Concurrent (n = 7), before (n = 4), after (n = 10), unknown (n = 4)	Melanoma	Brain	Advanced metastatic	NR	N	N
Hiniker et al. [40]	2012	Case report	1 (2)	54/3	Ipilimumab, 3 mg/kg i.v./3 w	Concurrent	Melanoma	Liver	Advanced metastatic	NR	N	N
Qin et al. [36]	2016	Retrospective	44 (NR)	20/1–5	Ipilimumab, dosage NR	Before (n = 24) or after (n = 20) median 9.6 w (range 0–162 w)	Melanoma	Brain, body (site NR)	Advanced metastatic	17.6	NR	NR
Patel et al. [35]	2015	Retrospective	20 (NR)	15, 18, 21/1–5	Ipilimumab, 3 mg/kg i.v./3 w	Concurrent (n = 1), before (n = 12), after (n = 7) median 40 d (range 0–117 d)	Melanoma	Brain	Advanced metastatic	7.3	NR	NR
Alomari et al. [41]	2016	Case report	1 (6)	20/1	Nivolumab, dosage NR	Start 1 m after SBRT	Lungcancer	Brain	Advanced metastatic	NR	Y	Y
Ahmed et al. [42]	2016	Retrospective	26 (73)	21/1–5	Nivolumab, dosage NR	Concurrent (n = 5), before (n = 35) median 1 m (range 0.4–4.5 m), after (n = 33) median 3 m (range 1–6 m)	Melanoma	Brain	Advanced metastatic	9.4	Y	Y

included NSCLC patients. No studies with concurrent lapatinib were found.

Regarding cranial SRT, Schwer et al. performed a Phase 1 trial in 15 patients for recurrent glioma treated with gefitinib and SRT, which showed no severe toxicity [49]. Kim et al. retrospectively analysed SRT combined with gefitinib or erlotinib for NSCLC brain metastases in 18 patients and observed no severe toxicity [48]. Weickhardt et al. also did not observe severe toxicity in 7 patients treated with erlotinib or crizotinib and cranial SRT [50].

Regarding extra-cranial SRT, the prospective study of Wang et al. used SRT to treat a maximum of 3 lung metastases in stage IV NSCLC patients (n = 14) with concurrent gefitinib [51]. Grade 3 toxicity possibly caused by the concurrent treatment occurred in 4 patients (29%), consisting of stomatitis, esophagitis, and radiation pneumonitis (n = 3) (Table 2). One patient received a dose reduction of gefinitib because of toxicity. Iyengar et al. prospectively treated extra-cranial NSCLC metastases with concurrent erlotinib and SRT; 29 severe toxicity events were observed in 24 patients, of which 4 were definitely attributed to SRT. These include one grade 4 toxicity described as hypoxia that resulted in a grade 5 ARDS/pneumonia in the same patient, and 2 grade 3 toxicity events, described as vertebral body compression and radiation pneumonitis. The 12 deaths were described as not related to concurrent therapy [47]. Weickhardt et al. did not observe any severe toxicity in their retrospective study of SRT and concurrent erlotinib in 10 patients with NSCLC [50].

In summary, concurrent EGF-R-targeting TKIs and extra-cranial SRT might be associated with increased toxicity within the irradiated volume in the treatment of abdominal and thoracic metastases; however, no increased toxicity was observed in cranial SRT. Data about the combination of lapatinib with SRT is not available.

ALK-Inhibitors (crizotinib, ceritinib, alectinib)

Only 2 retrospective studies, treating a total of 29 patients with concurrent crizotinib and SRT for oligoprogressive NSCLC in cranial and extra-cranial metastases, were found (Table 1a). Gan et al. performed SRT with a range of 12 to 54 Gy in 1–3 fractions [52]; Weickhardt et al. did not describe detailed SRT doses. In both studies, crizotinib was paused during SRT treatment [50]. No severe toxicity was observed (Table 2).

In summary, available data does not allow for a robust conclusion on safety of combined crizotinib, ceritinib, alectinib and SRT.

BRAF-Inhibitors (vemurafenib, dabrafenib)

Toxicity of SRT combined with BRAF-inhibitors was reported in 10 studies (Table 1b). All studies performed radiosurgery (mean dose ranging from 18 to 27 Gy) for melanoma brain metastases; of these, one was a prospective study [53], 6 were small retrospective studies [4,54–58], and 3 were case reports [59–61]. A total of 20 severe toxicity events in 75 patients were observed (27%) (Fig. 3a): intratumoral haemorrhage (n = 11), headache (n = 2) and cerebral oedema (n = 7). Overall, severe grade 3/4 cerebral oedema was observed in 15% of patients (Table 2). The study of Narayana et al. additionally described two deaths caused by cerebral oedema, but did not mention specifically whether this was radiotherapy-related, nor whether these patients received concurrent treatment with WBRT or SRT [57]. None of the 10 SRT studies reported severe skin toxicity, which is in contrast to experiences from conventionally fractionated radiotherapy.

Two studies compared intratumoral haemorrhage after SRT with concurrent BRAF-inhibitors to SRT alone [53,56]. Ly et al. found an increased risk of haemorrhage (61% vs. 23%, no statistical analysis) in their retrospective study of 17 patients, in which SRT was performed with a median of 20 Gy in 1 fraction and BRAF-inhibition was paused during SRT. In contrast, Wolf et al. showed

Table 2
Toxicity as observed within the included articles.

Targeted therapy	Study	Patients (*n*)	Grade 3 (*n*)	Grade 4 (*n*)	Grade 5 (*n*)	Total toxicity (*n*)	Total toxicity within the irradiated volume (*n*)
Bevacizumab		215	37	10	0	47	13
	Cuneo et al. [20]	42	Radionecrosis, Fatigue, Headache, Changes in memory, Increase in seizure activity, Worsening of neurological symptoms (*n* = 4) No significanant difference to RT alone	NR	NR	4	4
	Gutin et al. [14]	25	Leukopenia (*n* = 2); Neutropenia (*n* = 2); Lymphopenia (*n* = 7); Thrombocytopenia (*n* = 2); Anaemia (*n* = 3); Hyponatremia (*n* = 6); Fatigue (*n* = 1); Hypertension (*n* = 1); CNS haemorrhage (*n* = 1)	Lymphopenia (*n* = 2); Thrombocytopenia (*n* = 1); Bowel perforation (*n* = 1); Gastrointestinal bleeding (*n* = 1); Wound-healing disorder (*n* = 1)	NR	31	2
	Wang et al. [16]	8	NR	NR	NR	0	0
	Yomo et al. [23]	5	Anaemia (*n* = 1); Gastrointestinal bleeding (*n* = 1)	NR	NR	2	0
	Minniti et al. [22]	26	Pulmonary embolism (*n* = 1); Wound dehiscence (*n* = 1)			2	1
	Omuro et al. [15]	40	NR	Renal failure (*n* = 1); Pulmonary embolism (*n* = 2); Surgical woundinfection (*n* = 1)	NR	4	1
	Cabrera et al. [13]	15	Headache (*n* = 1)	NR	NR	1	1
	Clark et al. [18]	21	Seizure (*n* = 1); Dysphasia (*n* = 1)	NR	NR	2	2
	Hasan et al. [21]	9	No Grade 2 or higher observed		NR	0	0
	Conde et al. [19]	9	No Grade 4 or higher observed				
	Cabrera et al.[24]	1	No toxicity observed		NR	0	0
	Barney et al. [17]	14	Gastric ulcer (*n* = 1)	Gastric perforation (*n* = 1)	NR	2	2
Trastuzumab		7	0	1	0	1	1
	Carlson et al. [32]	7	NR	Cerebral oedema (*n* = 1)	NR	1	1
Cetuximab		244	31	0	1	32	32
	Vargo et al. [28]	48	Mucositis (*n* = 1); Dermatitis (*n* = 1); Dysphagia (*n* = 2); Aerodigestive fistula (*n* = 2)	NR	NR	6	6
	Lartigau et al. [27]	56	Dermatitis (*n* = 5); Mucositis (*n* = 4); Dysphagia (*n* = 3); Dysgeusia (*n* = 1); Skin fibrosis (*n* = 1); Xerostomia (*n* = 1); Fistula (*n* = 1)	NR	Haemorrhage/ denutrition (*n* = 1)	17	17
	Vargo et al. [31]	72	⩾G3 acute toxicity significantly increased with addition of cetuximab (13% vs 10%, *p* = 0.008), no difference in late toxicity				
	Comet et al. [26]	15	Mucositis; Dysphagia; Induration/Fibrosis (*n* = 3)	NR	NR	3	3
	Heron et al. [29]	35	Dysphagia (*n* = 2); Xerostomia (*n* = 2); Dysgeuisia (*n* = 1)	NR	NR	5	5
	Quan et al. [30]	18	Mucositis (*n* = 1)	NR	NR	1	1
Ipilimumab		121	7	1	0	8	4
	Kiess et al. [33]	15	Pruritus (*n* = 1); Hepatitis (*n* = 1); CNS haemorrhage (*n* = 2); Seizure (*n* = 2)	Cardiopulmonary (*n* = 1)	NR	7	4
	Golden et al. [39]	1	NR	NR	NR	0	0
	Tazi et al. [38]	10	Diarrhea (*n* = 1)	NR	NR	1	0
	Silk et al. [37]	5	No increased toxicity compared to SRT alone (12.5% SRT vs. 3.9% SRT + ipilimumab, intratumoral haemorrhage, grading NR)				
	Mathew et al. [34]	25	NR	NR	NR	0	0
	Hiniker et al. [40]	1	NR	NR	NR	0	0
	Qin et al. [36]	44	No increased toxicity compared to ipilimumab alone (37 toxicities (ipilimumab) vs. 33 toxicities (SRT + ipilimumab), unreported grading); pyrexia (*n* = 1); nausea (*n* = 4); fatigue (*n* = 5); anorexia (*n* = 2); dermatologic (*n* = 12); GI (*n* = 8); endocrine (*n* = 1)				
	Patel et al. [35]	20	Trend towards higher rates of radiation necrosis compared to SRT alone (30% vs. 21%, ns), no difference in haemorrhage, grading NR				

Table 2 (*continued*)

Targeted therapy	Study	Patients (*n*)	Grade 3 (*n*)	Grade 4 (*n*)	Grade 5 (*n*)	Total toxicity (*n*)	Total toxicity within the irradiated volume (*n*)
Nivolumab		27	2	1	0	3	3
	Alomari et al. [41]	1	NR	Cerebral oedema ($n = 1$)	NR	1	1
	Ahmed et al. [42]	26	Cerebral oedema ($n = 2$)	NR	NR	2	2
Sorafenib/sunitinib		137	43	4	2	49	7
	Staehler et al. [44]	106	Hypertension (4%); Rash (1%); Mucositis (1%); Diarrhea (1%); Thrombocytopenia (2%); Anaemia (11%); Hand-foot-Syndrome (1%); Myocardial infarction (2%); Thrombosis (1%)	NR	Cerebral haemorrhage ($n = 1$)	25	0
	Brade et al. [45]	16	Thrombocytopenia ($n = 4$); Neutropenia ($n = 1$); Confusion ($n = 1$); Liver enzyme changes ($n = 2$), Lower GI haemorrhage ($n = 1$)	Liver enzyme changes ($n = 1$); Small bowel obstruction ($n = 1$)	Upper GI haemorrhage ($n = 1$)	12	6
	Straka et al. [46]	1	NR	NR	NR	0	0
	Ahluwalia et al. [43]	14	Fatigue($n = 5$); Neutropenia ($n = 1$); Haemolysis ($n = 1$); Stomatitis ($n = 1$); Generalized muscle weakness ($n = 1$); Rash ($n = 1$)	Neutropenia ($n = 1$); Lymphopenia ($n = 1$)	NR	12	1
Gefitinib/erlotinib		81	32	4	1	37	8
	Wang et al. [51]	14	Skin acne ($n = 1$); Stomatitis ($n = 1$); Esophagitis ($n = 1$); Diarrhea ($n = 1$); Radiation pneumonitis ($n = 3$); Fatigue ($n = 1$)	NR	NR	8	4
	Schwer et al. [49]	15	NR	NR	NR	0	0
	Kim et al. [48]	18	NR	NR	NR	0	0
	Iyengar et al. [47]	24	Total ($n = 24$); of which SRT related: Vertebral body compression ($n = 1$); Radiation pneumonitis ($n = 1$)	Diarrhea ($n = 1$); Fatigue ($n = 1$); Motor neuron neuropathy ($n = 1$); SRT-related: Hypoxia ($n = 1$)	Total ($n = 13$); of which SRT related: ARDS/pneumonia ($n = 1$)	24	4
	Weickhardt et al. [50]	10	NR	NR	NR	0	0
Crizotinib		29	0	0	0	0	0
	Gan et al. [52]	14	NR	NR	NR	0	0
	Weickhardt et al. [50]	15	NR	NR	NR	0	0
Vemurafenib/ dabrafenib		129	19	1	0	20	20
	Ahmed et al. [54]	24	Haemorrhage ($n = 1$)	NR	NR	1	1
	Peuvrel et al. [60]	1	Headache ($n = 1$)	NR	NR	1	1
	Narayana et al. [57]	6	No intracranial bleeding and no $\geqslant$ Gr3 cutaneous toxicity observed				
	Ly et al. [56]	17	Increased haemorrhage risk associated with BRAF-inhibitors (61% vs 23%)				
	Liebner et al. [59]	2	Headache ($n = 1$)	Cerebral oedema ($n = 1$)	NR	2	2
	Stefan et al. [61]	1	NR	NR	NR	0	0
	Gaudy et al. [55]	24	Cerebral oedema ($n = 6$); Haemorrhage ($n = 10$)	NR	NR	16	16
	Wolf et al. [53]	31	No significant difference in haemorrhage to RT alone (18% haemorrhage of unreported grading for concurrent therapy)				
	Hecht et al. [4]	19	NR	NR	NR	0	0
	Patel et al. [58]	4	No increased or unexpected neurologic nor cutaneous toxicity with administration of SRS				
Trametinib		4	0	0	0	0	0
	Patel et al. [58]	4	No increased or unexpected neurologic nor cutaneous toxicity with administration of SRS				

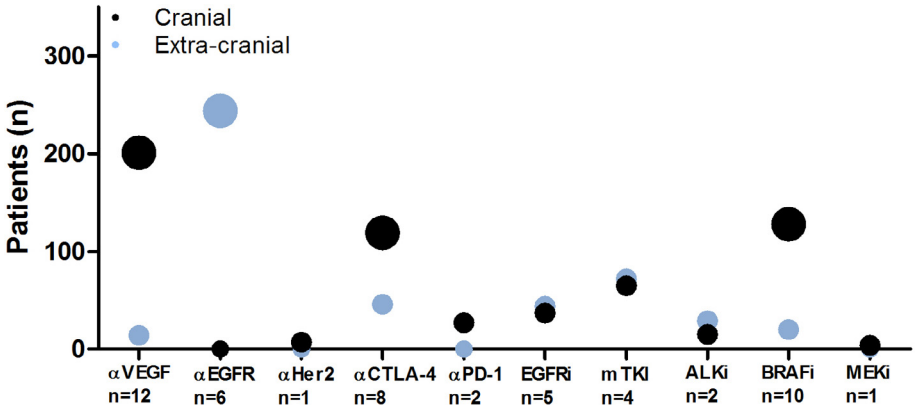

Fig. 2. Included studies and patients; X-axis: *n* = number of included studies. Size of the circle is proportional to the number of patients analysed (0, <100, ⩾100).

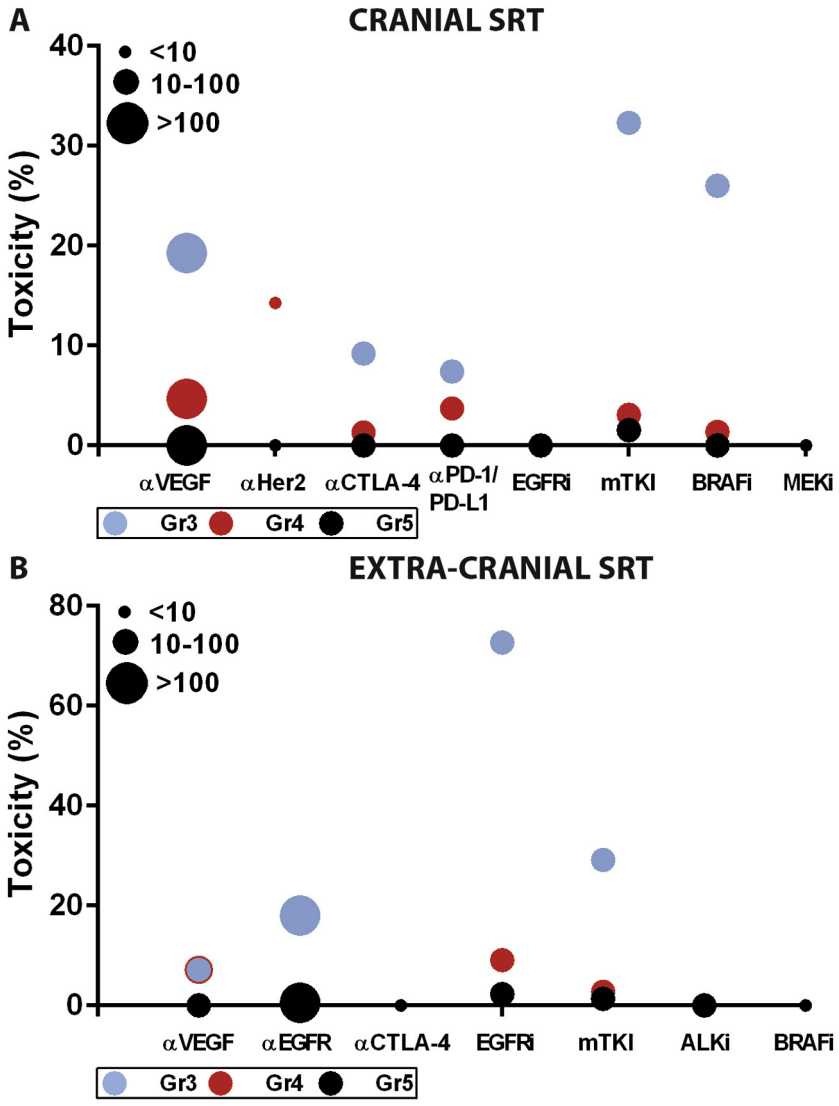

Fig. 3. Cranial vs. extra-cranial severe toxicity evaluated per different targeted therapy class; (A) Cranial SRT; (B) Extra-cranial. Toxicity percentage is calculated as the number of toxicity events per treated patients. The size of the circle represents the size of the patient population.

no significant difference in haemorrhage (16% after BRAF & SRT vs. 8% after SRT, ns), after performing SRT with 18G in 1 fraction. Both studies did not report the severity of haemorrhage. While the studies of Ahmed et al. and Gaudy et al. observed grade 3 haemorrhage in a total of 11 of 48 patients (23%) [55] [54], the remaining 6 studies did not observe intratumoral haemorrhage (Table 2).

In summary, data on CNS toxicity after combined cranial SRT and BRAF-inhibitors is conflicting. However, high rates of toxicity

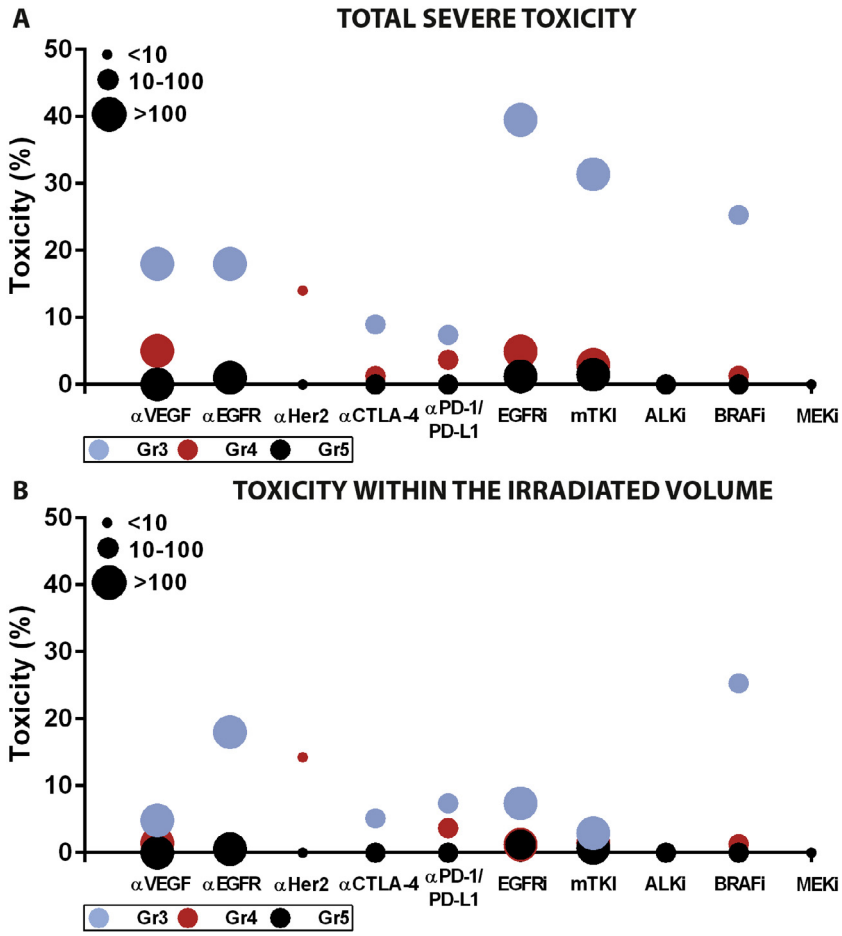

Fig. 4. Total severe toxicity vs. toxicity within the irradiated volume evaluated per different targeted therapy class; (A) Totally observed toxicity; (B) SRT-attributed toxicity. Toxicity percentage is calculated as the number of toxicity events per treated patients. The size of the circle represents the size of the patient population.

reported in some studies warrant caution. There is no data on the combination of BRAF inhibitors and extra-cranial SRT.

MEK-inhibitors (trametinib)

Currently, only Patel et al. evaluated the toxicity of concurrent BRAF-, and MEK-inhibitor therapy with SRT [58]. This small retrospective study included only 4 patients with melanoma brain metastasis that were treated with SRT and concurrent targeted therapy. Median SRT dose was 21 Gy in 1 fraction and trametinib was pasued 2–3 days before and after SRT, or it was initiated within 1 month after SRT, with a median of 21 Gy in 1 fraction. They did not observe any severe toxicity within a median follow-up of 10.6 months.

In summary, the very small number of patients treated with combined SRT and MEK inhibitors does not allow to draw any conclusions about its safety.

Discussion

This review shows that even though concurrent treatment with SRT and targeted drugs or immunotherapy is increasingly performed, available safety information is primarily based on small, retrospective single institution experiences. Combined modality treatment was most frequently studied in patients with brain metastases or recurrent glioblastoma; substantially less data is available for extra-cranial SRT.

In general, cranial SRT and concurrent targeted therapy is well tolerated for the majority of evaluated targeted therapies. The best safety data is available for SRT combined with bevacizumab, ipilimumab, nivolumab and EGFR-targeting TKIs. Bevacizumab may possible even prevent SRT-induced radionecrosis [16]. Severe neurotoxicity was mainly, but not consistently, reported when cranial SRT was combined with BRAF-inhibitors (vemurafenib, dabrafenib); it is unclear whether this variability reflects differences in the practice of cranial SRT regarding radiotherapy dose, volume and number of treated lesions or is simply the result of bias given the retrospective nature of the studies. Interestingly, no severe skin toxicity was observed, as known from the combination of vemurafenib and conventionally fractionated radiotherapy. Severe toxicity observed after cranial SRT combined with bevacizumab, sunitinib and sorafenib was primarily based on extra-cranial events attributed to the systemic treatment, and not SRT.

Based on the more limited data of extra-cranial SRT concurrent with targeted/immunotherapy, we found some indications of a potentially increased risk of severe toxicity when extra-cranial SRT was combined with bevacizumab, sorafenib, cetuximab and EGFR-targeting TKIs. Interestingly, EGFR-targeting TKI-therapy was well tolerated when combined with cranial SRT, but not with extra-cranial SRT. For ALK- targeting crizotinib in patients with metastatic NSCLC, no severe toxicity was observed in any study of concurrent treatment with extra-cranial SRT. This emphasizes that combination strategies of extra-cranial SRT are not universally associated with increased risks but all combinations need to be evaluated individually. However, for many targeted therapies (e.g. pembrolizumab, alectinib, ceritinib, panitumumab, lapatinib), so far no experiences of combined modality treatment have been published.

This review has several limitations, which mainly reflects the status of our current knowledge of concurrent treatments. We focused on severe toxicity. In the search process, many studies had to be excluded because toxicity was not clearly defined or described. This is unfortunately a known problem in radiation oncology research [62]. Furthermore, we observed that the available studies did not use a consistent definition of concurrent treatment. We therefore chose to define concurrent therapy as targeted therapy combined with SRT within one month of SRT. Studies that shortly paused targeted therapy during SRT were included, as the half-life of targeted therapy and especially immunotherapy is often long (range 24 h – 50d) and several targeted therapies and immunotherapies are administered once every 2 or 3 weeks, so that treatment is concurrent even though not given at the same day.

In conclusion, cranial SRT was well tolerated when combined with the majority of targeted drugs and immunotherapy but the combination with BRAF-Inhibitors should be practiced with caution. Extra-cranial SRT was associated with higher risks when combined with bevacizumab, sorafenib, cetuximab and EGFR-targeting TKIs. However, this review also exposed multiple scenarios where no data regarding safety is available. Nevertheless, it is expected that concurrent SRT and targeted therapies will be increasingly performed. As the design of homogeneous prospective trials examining safety is complicated by the rapidly growing number of available targeted agents and hugely divers combined treatment strategies, a potential solution to generate better and quicker knowledge could be the establishment of prospective registry databases.

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