Review Article | Symptom Management in Palliative Medicine and Palliative Care

Hemostatic radiotherapy: a narrative review of the literature

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Background and Objective: In locally advanced cancer, bleeding is a common clinical presentation and radiotherapy (RT) provides a noninvasive, well-tolerated, cost-effective treatment. However, the choice for fractionation dose and schedule seem to merely depend on physician's preference rather than specific guidelines. We reviewed the available literature on palliative hemostatic RT for response rate (RR) and bleeding duration in relation with the given dose.

Methods: The PubMed database was used to search for articles, which were assessed by predetermined inclusion and exclusion criteria. A total of 54 articles, published over the last 20 years until December 2023 were analyzed for dose and/or fractionation regimen and their relation to the RR.

Key Content and Findings: A variety of fractionation schedules are used for palliative symptom control, including hemostasis. Research focusing on hemostatic irradiation specifically and prospective studies are rare. Moreover, to our knowledge, there are no specific (prospective) studies ongoing. Both external beam radiotherapy (EBRT) and brachytherapy lead to bleeding control and daily or weekly hypofractionated irradiation is safe and effective for both high and low biological equivalent dose (BED) regimens. If feasible, based on patient condition, some studies favor higher BED regimens to obtain more durable tumor/higher bleeding response. Higher radiation dose for thoracic irradiation may be indicative for simultaneous presentation of obstruction and/or dysphagia. Brachytherapy may be used solely or in combination with EBRT or in the setting of re-irradiation. Short-course regimens are preferred in patients in with low performance index scores. For future studies, multivariate analysis, including BED, can be important to assess efficacy of different fractionation schedules for a variety of tumor etiologies.

Conclusions: Hemostatic RT, both by EBRT and brachytherapy, appears to be a safe and effective palliative treatment that clinically and statistically significantly reduces bleeding in cancer patients. The available literature is limited regarding prospective and uniform evaluation of hemostatic RT, including fractionation schedules. BED seems to be indicative for a better RR for specific indications. Current evidence suggests that treatment decisions should be tailored according to the patients' condition, tumor etiology and other clinical symptoms. More (prospective) research focusing on hemostasis is necessary to develop clear guidelines.

Keywords: Hemostatic radiotherapy; palliative radiotherapy; palliative treatment; brachytherapy

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Introduction

Up to 10% of patients with (locally) advanced cancer will experience a form of acute bleeding at some point during their disease trajectory (1). Bleeding tumors can present in a variety of ways, as a presenting symptom or develop during disease progression. It can appear from chronic occult bleeding to clinically significant macroscopic or even profound bleeding from large blood vessels.

Depending on the bleeding site, symptoms can vary and include hematemesis, hemoptysis, hematuria, hematochezia, epistaxis, vaginal or rectal or skin ulcer bleeding. Clinically significant bleeding can have a negative impact on the quality of life (QoL) of both patients and their families due to distress, anxiety, physical deterioration and/or the need for hospitalization. For some patients, acute bleeding will even be the direct cause of death.

In palliative setting, there is a wide variety of indications for radiotherapy (RT), tumor bleeding being just one of them. RT is regarded as a relatively noninvasive, well-tolerated, cost-effective treatment strategy in hemorrhagic control, with a good reported treatment response (i.e., bleeding stops or significantly diminishes) (2-4). The hemostatic effectiveness of RT appears usually after only a few fractions and is a consequence of both tumor response and an upregulation of the hemostatic cascade (5,6). Tumor remission combined with the effect of radiation induced platelet aggregation and vessel fibrosis due to vascular endothelial cell damage following induces hemostasis.

Although RT has been used for decades for cancer related bleeding, there is little literature specifically focusing on hemostatic RT. Consequently, an array of different fractionation schedules exists, varying from short one-fractionated to multiple fraction regimens with relatively low- to very-high-dose prescriptions per fraction. In addition, the presence of complaints other than bleeding, such as pain, obstruction, dysuria, frequency or cough for example, and the aim to reduce tumor volume can also influence the chosen fractionation and total dose.

Therefore, this review explores the available literature on hemostatic RT in the palliative setting, reporting on response rate (RR) and duration for bleeding in relation to the given dose and biological equivalent dose (BED). We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-24-26/rc).

Methods

Our search identified 6,696 results over the last 20 years. First, duplicates were removed, followed by title and abstract screening by two independent researchers (P.V. and E.O.). Conflicts were resolved in discussions with a third researcher (M.C.). The PRISMA search strategy and the search strategy summary with selection criteria are provided in *Figure 1* and *Table 1*. The search summary table is provided in *Table 2*.

Second, full text was assessed based on predetermined selection criteria (*Table 1*). Articles were evaluated based on their reports on RT in the hemostatic setting, using a palliative RT fractionation schedule. The use of external beam radiotherapy (EBRT) and/or brachytherapy (BT) was allowed. All reviews, case reports, studies and small case cohorts were excluded, as were studies that did not report on fractionation schedule, oncological indication or made use of a co-intervention with other hemostatic agents or treatments other than standard systemic treatment. At least 30% of the patient population in the accepted studies had to present with bleeding symptoms requiring palliative treatment.

After applying the exclusion criteria, a total of 54 articles remained for final review. Extracted data included first author, year of publication, study design, country, sample sizes, tumor location, primary tumor, fractionation schedule (median/mean BED and/or dose, and/or minimum and maximum total dose with number of fractions), outcome criteria, use of chemotherapy (prior, during or adjuvant to RT), time to re-bleeding or event-free survival, overall response rate (ORR) or symptom relief. Due to the many different study designs, primary tumor histology, treated localization and study endpoint no meta-analysis was conducted.

Results

The 54 articles included in our review are shown in *Table 2*. Of the included studies, 45 were retrospective (83.3%) and 9 were prospective (16.7%), including one phase I trial and three phase II trials. We found seven studies that focused on

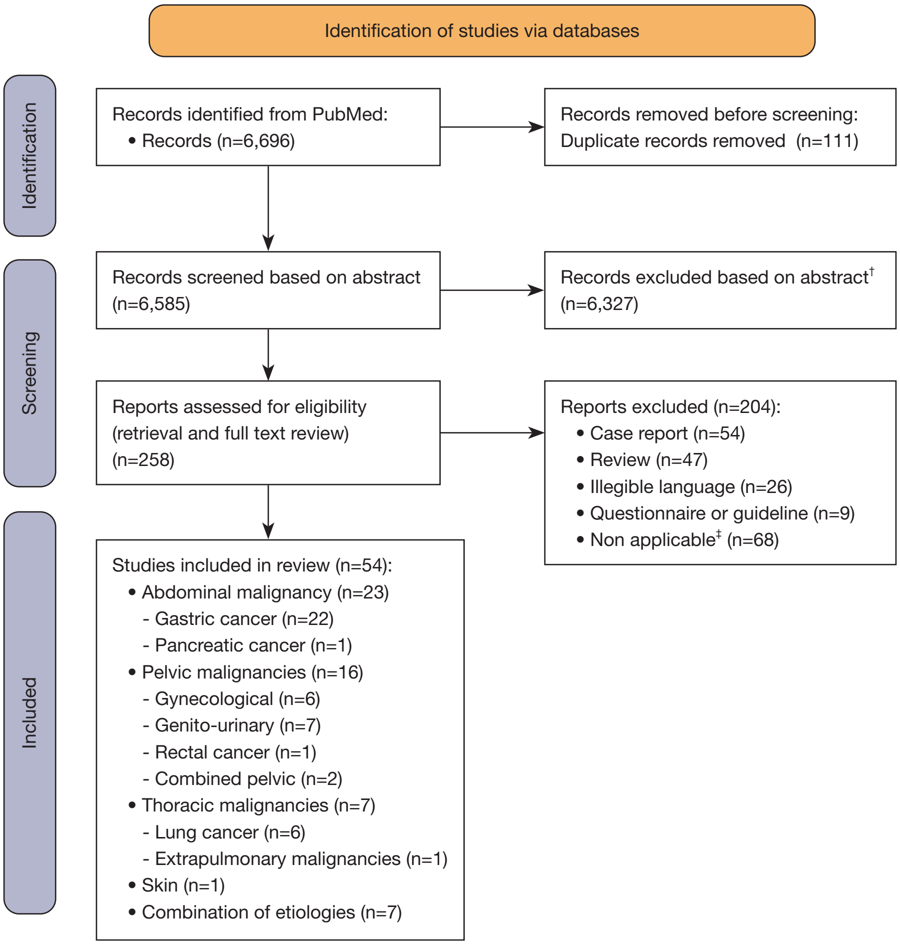

Figure 1 PRISMA flowchart of screening procedure and identified studies for inclusion. †, no automation tools were used, all records were excluded by a human; ‡, insufficient ratio in number of hemostatic patients in the cohort, non-applicable palliative hemostatic schedules/radiation doses, no diagnosed malignancy, curative intent, no radiotherapy used, no available abstract.

BT with or without EBRT. The majority of studies found were performed in Asia (63%).

Abdomen

Nearly half the studies found [n=22 (40.7%)], reported on the effect of EBRT on gastric bleeding (*Table 2*). The four oldest studies on this topic were retrospective and all evaluated hemostatic RT in advanced, unresectable gastric cancer (7-10). The studies from Tey *et al.* and Lee *et al.* evaluated clinical RR for fractionation schedules of median 30 Gy/10 fractions (fr) to vary between 54% and 92% respectively (7,10). Kim *et al.* reported better local control at 6 months in treatment groups receiving a BED_{10} >41 Gy (8). Overall, the median event-free survival of their patient group was higher compared to the other studies, probably because 2/3 of patients received concurrent chemotherapy. Hashimoto *et al.* reported a highly successful hemostatic effect in 92% of patients (9). Received dose in the treatment success group (median 40 Gy) was significantly higher than the failure group (median 19 Gy) (P=0.026) and BED_{10} ≥50 Gy, corresponding 40 Gy/16 fr, was significantly correlated with treatment success (P=0.04).

Several studies tried to link the (duration of) the palliative effect to the dose given, often expressed in BED_{10} with α/β of 10. Tey *et al.* did not see any difference between doses below or exceeding BED_{10} 39 Gy (7). However, Kim *et al.* supported a higher BED in favor of local control and Hashimoto *et al.* reported a significant correlation with treatment success in their BED_{10} group over 50 Gy (8,9).

Table 1 Search strategy summary

Items	Specification
Date of search	January 2024
Databases and other sources searched	PubMed
Search terms	MeSH terms: “hemostasis”, “hematuria”, “bleeding”, “hemorrhage”, “hematemesis”, “hemoptysis”, “radiotherapy”, “radiation therapy”, “radiation treatment”, “brachytherapy”, “curie therapy”, “surface radiotherapy”, “intracavity radiotherapy”, “interstitial radiotherapy”, “implant radiotherapy”
	Filter: published in the last 20 years
Timeframe	Twenty years (January 2003–December 2023)
Inclusion and exclusion criteria	Exclusion
	• Reviews, case reports, studies and small case cohorts
	• Fractionation schedule unknown/not clear
	• Limited patient with bleeding symptom (<30%)
	• Non-malignant indication
	• Co-intervention, other than systemic oncologic treatment
	Inclusion
	• Published in English/Dutch
	• Palliative setting with hemostatic intent
Selection process	Title and abstract screening: Two independent researchers (P.V. and E.O.)
	Full text screening: Two independent researchers (P.V. and E.O.)
	Consensus: Discussion with third researcher (M.C.)
Additional considerations, if applicable	All studies in this review were published over the last 20 years until December 2023

The study from Lee *et al.* from 2017 found a significantly higher median BED_{10} of 45 Gy for treatment responders compared to non-responders, median BED_{10} 26.4 Gy (P<0.001) and presented a cut-off dose of BED_{10} 36 Gy to separate both groups (P<0.001) (11). BED and bleeding response were associated in univariate analysis but were negatively correlated and co-founded by the palliative prognostic index (PPI), a survival predictor in critically ill cancer patients (12,13). Lower BED regimens for patients with higher PPI resulted in higher probability of death and less chance of bleeding response compared to patients with lower PPI receiving more aggressive (high BED) hemostatic treatment.

The retrospective trial of Tey *et al.* from 2014 included the highest number of patients in studies regarding gastric cancer (n=103) (14). Their trial used mainly three different fractionation regimens (*Table 2*), where 67% of patients received BED_{10} ≤39 Gy and 33% >39 Gy without significantly different RR for bleeding (P=0.78). However, there was tendency in favor of higher BED fractionation schedules (P=0.12), to solve concurrent symptoms such as obstruction and pain. A study that compared short course palliative schedules (8 Gy/1 fr; BED_{10} 14.4 and 20 Gy/5 fr; BED_{10} 28 Gy) found a tendency towards better RR and overall survival (OS) with a median survival of 5.1 *vs.* 8.0 months in the higher BED_{10} group (P=0.202) (15).

A retrospective study, published after 2020, showed for patients who received a dose BED_{10} >39 Gy a hemostasis of 71.1% compared to 32.4 % in patients who received a lower BED_{10} (P<0.001) (16). For a total BED_{10} 37.5 Gy, the group of Lee *et al.* found no significant difference regardless of the fraction dosage (4 Gy or more) or the number of fractions (5 or less) (17). Median rebleeding free survival was 6.4 weeks, based on Hb measurement or blood transfusion need (BTN) as indicators for rebleeding after irradiation (17). Of all

Table 2 Search summary table, different studies with varying fractionation regimens and response rate

Study	Year of publication	Retro/prospective	Country	Number of patients	Cancer etiology	Localisation	Fractionation schedule [range]	Outcome	Systemic treatment (prior, concurrent, adjuvant)	Time to rebleeding (months), median [range]	Overall response rate
Tey *et al.* (7)	2007	R	Singapore	24	Gastric cancer	Abdomen	30 Gy/10 fr (71%) [8–40 Gy/1–16 fr]	Hb level and clinical response	No systemic treatment	4.5	54%
Kim *et al.* (8)	2008	R	USA	20	Gastric cancer	Abdomen	35 Gy/14 fr [20–36 Gy]: BED <41 Gy (49%); BED >41 Gy (51%)	Symptomatic clinical response	65% concurrent 41% adjuvant	11.4	70%
Hashimoto *et al.* (9)	2009	R	Japan	19	Gastric cancer	Abdomen	40 Gy/16 fr [20–50 Gy/10–25 fr]	Endoscopic control, Hb level and performance score	21% concurrent 37% adjuvant	3.4	91% (68.4% CR)
Lee *et al.* (10)	2009	R	Korea	23	Gastric cancer	Abdomen	30 Gy/10 fr	BTN, Hb level and clinical response	61% prior	3.7 [0.5–15.2]	91%
Lee *et al.* (11)	2017	R	Korea	42	Gastric cancer	Abdomen	39.6 Gy/20 fr [14–50.4 Gy/7–28 fr]	Clinical response	69% prior 16.7% concurrent	3.7	69%
Saito *et al.* (12)	2022	P: observational	Japan	50	Gastric cancer	Abdomen	8 Gy/1 fr (21%) 20 Gy/5 fr (32%) 30 Gy/10 fr (38%) [8–45 Gy/1–18 fr]	Hb level and bleeding control	65% prior 35% no systemic treatment	2.3	69–90%
Sugita *et al.* (13)	2022	R	Japan	33	Gastric cancer	Abdomen	30 Gy/10 fr (76%) 20 Gy/5 fr (12%) BED <39 Gy (24%)	Hb level and BTN	45% adjuvant	4.9	73%
Tey *et al.* (14)	2014	R	Singapore	103	Gastric cancer	Abdomen	30 Gy/10 fr (40%) 20 Gy/5 fr (16.5%) 36 Gy/12 fr (33%) [8–40 Gy/1–16 fr]	BTN and gastroscopic evaluation	7.8% prior 8.7% adjuvant	3.3	80.60%
Chaw *et al.* (15)	2014	R	Scotland	52	Gastric cancer	Abdomen	8 Gy/1 fr (75%) 20 Gy/5 fr (25%)	Hb level and BTN	14% prior	NA	50%
Takeda *et al.* (16)	2022	R	Japan	117	Gastric cancer	Abdomen	30 Gy/10 fr (64.2%) 20 Gy/5 fr (19.2%)	Hb level, BTN and clinical response	NA	NA	59.6% in total BED >39 Gy (71.1%) BED <39 Gy (32.4%)
Lee *et al.* (17)	2021	R	Korea	57	Gastric cancer	Abdomen	25 Gy/5 fr (29.8%) 20 Gy/5 fr (24.6%) 30 Gy/10 fr (22.8%) [17.5–45 Gy/4–25 fr]	Clinical response, endoscopic assessment and Hb level	75.4% prior 17.5% concurrent 47.4% adjuvant	1.6 [0–60]	75.4% (30.2% CR)
Tey *et al.* (18)	2019	P: phase 2 trial	Singapore & China	50	Gastric cancer	Abdomen	36 Gy/12 fr	BTN and clinical response	10% prior 14% adjuvant	3.4 [0–34.4]	80%
Tanaka *et al.* (19)	2020	P	Japan	31	Gastric cancer	Abdomen	20 Gy/5 fr; 15 Gy/5 fr (re-irradiation)	Hb level	32% adjuvant	2 [1–6.3]	80.60%
Andleeb *et al.* (20)	2023	R	India	78	Gastric cancer	Abdomen	30 Gy/10 fr (54.1%) 20 Gy/5 fr (29.7%) 15 Gy/3 fr (16.2%)	Clinical response, BTN and Hb level	64.48% prior	NA	70.27%

Table 2 (*continued*)

Table 2 (*continued*)

Study	Year of publication	Retro/prospective	Country	Number of patients	Cancer etiology	Localisation	Fractionation schedule	Outcome	Systemic treatment (prior, concurrent, adjuvant)	Time to rebleeding (months), median [range]	Overall response rate
Asakura *et al.* (21)	2011	R	Japan	30	Gastric cancer	Abdomen	30 Gy/10 fr	BTN	40% concurrent 63% adjuvant	3.3	73%
Hiramoto *et al.* (22)	2018	R	Japan	23	Gastric cancer	Abdomen	42 Gy/20 fr [18–60 Gy/9–30 fr]	BTN	65.2% prior 43.5% concurrent 34.8% adjuvant	3.4	88.80%
Kawabata *et al.* (23)	2022	R	Japan	20	Gastric cancer	Abdomen	30 Gy/10 fr (80%) [10.5–30 Gy/3–10 fr]	BTN at 1 month and Hb level	25% prior 5% adjuvant	12 [0.5–22.7]	95%
Kondoh *et al.* (24)	2015	R	Japan	17	Gastric cancer	Abdomen	30 Gy/10 fr (67%) 40 Gy/20 fr (13%) 36 Gy/18 fr (13%) 30 Gy/12 fr (6%)	Hb level, symptomatic clinical response and BTN	73% prior 33% concurrent	0.9 [0–3]	73%
Mitsuhashi *et al.* (25)	2021	R	Japan	28	Gastric cancer	Abdomen	30 Gy/10 fr (61%) [20–40 Gy/5–20 fr]	Hb level and BTN	54% prior 10% concurrent 14% adjuvant 43% no systemic treatment	3.2 [1.7–4.5]	1-year blood transfusion free survival 69.4%
Yu *et al.* (26)	2021	R	Korea	61	Gastric cancer	Abdomen	30 Gy/10 fr [12.5–50 Gy/4–25 fr]	Clinical response, Hb level and BTN	82% prior 49.2% adjuvant	6	88.50%
Yagi *et al.* (27)	2023	R	Japan	25	Gastric cancer	Abdomen	39 Gy/13 fr 30 Gy/10 fr	Clinical response	68% adjuvant	NA	88%
Kawabata *et al.* (28)	2017	R	Japan	18	Gastric cancer	Abdomen	6 Gy/3 fr (66%) 12 Gy/6 fr (27%) 24 Gy/12 fr (5%)	Hb level and clinical response	72% prior 11% concurrent 44% adjuvant	1.3 [0.5–7.4]	55%
Shibuki *et al.* (29)	2023	R	Japan	20	Pancreatic cancer	Abdomen	30 Gy/10 fr (20%) 20 Gy/5 fr (70%) 8 Gy/1 fr (10%)	HB level and BTN	50% prior 50% adjuvant	NA	70%
Thurairaja *et al.* (30)[†]	2008	R	UK	23	Prostate cancer	Pelvis	24 Gy/4 fr (78%) 9–18 Gy/1–2 fr (22%)	Clinical (macroscopic) response	NA	NA	83% (91% after retreatment)
Lacarrière *et al.* (31)	2013	R	France	32	Bladder cancer	Pelvis	30 Gy/10 fr (41%) 20 Gy/5 fr (59%)	CTCAE score, grade 1	NA	3.6 [0–42]	68.75% (at 2 weeks 31% (at 6 months)
Zhang *et al.* (32)	2020	R	Japan	25	Urothelial cancer: bladder (21%)	Pelvis	20 Gy/5 fr (28%) 30 Gy/10 fr (68%) 40 Gy/2 fr (4%)	Hb level and BTN	56% prior 4% adjuvant	4.2 [0–23]	88% CR

Table 2 (*continued*)

Table 2 (*continued*)

Study	Year of publication	Retro/prospective	Country	Number of patients	Cancer etiology	Localisation	Fractionation schedule	Outcome	Systemic treatment (prior, concurrent, adjuvant)	Time to rebleeding (months), median [range]	Overall response rate
Ogita *et al.* (33)	2021	R	Japan	53	Bladder (41.5%) Prostate (30.2%) Upper GI (9.4%) Colorectal (9.4%) Gastric (3.8%) Esophageal (3.8%) Gynecological (5.7%)	Pelvis	30 Gy/10 fr (26%) 20 Gy/5 fr (23%) 36 Gy/12 fr (21%) [9–50 Gy/1–25 fr]	BTN and clinical response	41.5% prior or adjuvant 5.7% concurrent	4.3 (8.4 for macroscopic hematuria)	77.4% overall response (75.5% CR)
Dirix *et al.* (34)	2016	R	Belgium	44	Bladder cancer	Pelvis	34.5 Gy/6 fr (once weekly)	Clinical response	NA	13 [0.3–33.7]	89%
Coraggio *et al.* (35)	2020	R	France	26	Bladder cancer (85%) Prostate (15%)	Pelvis	Continuous regimen (54%): 30 Gy/3–10 fr Discontinuous regimen (46%): 23 Gy/4 fr (twice weekly over 3 weeks days 1-3-15-17)	Bleeding control	NA	NA	92%
Tey *et al.* (36)	2019	R	Singapore	58	Bladder cancer	Pelvis	BED <36 Gy (62%) BED ≥36 Gy (38%) [8–40 Gy/1–16 fr]	BTN and clinical response	8% prior	3.7	67% Low BED (61%) High BED (77%)
Butala *et al.* (37)	2021	R	USA	33	Uterus and cervix (72.7%) Ovary (15.2%) Vulva (6.1%) Vagina (6.1%)	Pelvis: gynecological	Median BED 37.5 Gy ≤5 fr (>3.5 Gy/fr) (54.5%) >5 fr (46.5%)	Clinical response	45% prior 18.1% concurrent	5.4	100% (84.8% CR)
Yan *et al.* (38)	2011	R	Canada	26	Uterus (35%) Cervix (25.4%) Ovarium (8%) Vulva (19.6%) Vagina (12%)	Pelvis: gynecological	21 Gy/3 fr [8–21 Gy/1–3 fr]	Clinical bleeding control	NA	NA	92% (61.5% CR)
Choan *et al.* (39)	2006	R	Canada	53	Ovarian cancer	Pelvis	30 Gy/10 fr [5–52.5 Gy/1–20 fr]	Clinical response	NA	4.8 [1–71]	100% (88% CR)
Jiang *et al.* (40)	2018	R	USA	33	Ovarian cancer	Pelvis	30 Gy/10 fr (29%) 20 Gy/5 fr (17%) 8 Gy/1 fr (8%) [7–53 Gy/1–28 fr]	Clinical response	97% prior	8.9	93% (80% CR)
Kim *et al.* (41)	2013	R	Korea	16	Cervix cancer	Pelvis	25 Gy/5 fr [20–25 Gy/4–5 fr]	Clinical response	NA	NA	93.80%
Mishra *et al.* (42)	2005	R	India	76	Uterine cancer	Pelvis: gynecological	10 Gy/1 fr (39%) 20 Gy/2 fr (28%) 30 Gy/3 fr (33%) (monthly)	Clinical response	NA	NA (only survival)	100%
Chia *et al.* (43)	2016	R	Singapore	83	Rectal cancer	Pelvis	30 Gy/10 fr [18–50 Gy/6–30 fr]	Clinical response	10% prior and/or adjuvant	5.4 [0–29.4]	86.70%

Table 2 (*continued*)

Table 2 (*continued*)

Study	Year of publication	Retro/prospective	Country	Number of patients	Cancer etiology	Localisation	Fractionation schedule	Outcome	Systemic treatment (prior, concurrent, adjuvant)	Time to rebleeding (months), median [range]	Overall response rate
Caravatta *et al.* (44)	2012	P: phase 1 clinical trial	Italy	13	Gynecological (48%) Colorectal (33.5%) GU (18.5%)	Pelvis: mixed	14 Gy/4 fr 16 Gy/4 fr 18 Gy/4 fr	Clinical response	10-day interval required	5 [1–12]	50% CR
Farina *et al.* (45)	2019	P: phase 2 trial	Italy	25	Endometrium (20%) Colon (20%) Prostate (12%) Bladder (12%) Ovarian (12%) Vulvar (8%) Rectum (8%) Bladder + prostate (8%)	Pelvis	18 Gy/4 fr (twice daily)	Bleeding resolution on RTOG patient evaluation	NA	NA	100% (58.3% CR)
Fleming *et al.* (46)	2017	R	USA	30	Lung cancer	Thorax	CFRT 30 Gy/10 fr (52%) SBRT 45 Gy/5 fr (48%)	Clinical response (symptom relief and local control)	NA	Recurrence: at 6 months: 52.4%; 1 year 6 months: 65.1%	86.60%
de Aquino *et al.* (47)†	2013	P	Brazil	28	Lung cancer (83.3%); other (16.7%)	Thorax	22.5 Gy/3 fr (75.4%) 15–20 Gy/5 fr (24.6%)	Speiser and Spratling score	38.5% in total	NA	100%
Mallick *et al.* (48)†	2006	P: phase 2 trial	India	45	Lung cancer	Thorax	EBRT 30 Gy/10 fr + HDREB: 16 Gy/2 fr (33.3%); 10 Gy/1 fr (33.3%) HDREB alone: 15 Gy/1 fr (33.3%)	Bronchoscopic evaluation and Speiser symptom score	NA	8	94.10% 100% in EBRT + BT 82% in EBRT only
Mallick *et al.* (49)†	2007	R	India	63	Lung cancer	Thorax	EBRT (30 Gy/10 fr) + HDREB: 16 Gy/2 fr (68.4%); 10 Gy/1 fr (15.8%) HDREB alone: 15 Gy/1 fr (15.8%)	Speiser and Spratling scale	NA	8	97% 100% (HDREB + EBRT) 83.3% (HDREB alone)
Siddiqui *et al.* (50)†	2023	R	Canada	25	Lung cancer	Thorax	HDREB: 14 Gy/2 fr weekly	Clinical response	NA	NA	88%
Donovan *et al.* (51)†	2017	P	Canada	17	Extrapulmonary malignancies: • Colorectal (25.7%) • Breast (14.3%) • Esophageal (8.6%) • Sarcoma (8.6%) • Lymphoma/myeloma (8.6%) • Renal (8.6%) • H&N (5.7%) • Cervix/testis (5.7%) • Hepatobiliary (5.7%)	Thorax	Brachytherapy: • Median 21 Gy/3 fr; 7 Gy/1 fr (20%); 14 Gy/2 fr (57%); 21 Gy/3 fr (41.43%) • EBRT: median 30 Gy/10 fr	Clinical response EORTC Quality of Life Questionnaire	NA	3 [1–8]	67.5% (11.8% CR)

Table 2 (*continued*)

Table 2 (*continued*)

Study	Year of publication	Retro/prospective	Country	Number of patients	Cancer etiology	Localisation	Fractionation schedule	Outcome	Systemic treatment (prior, concurrent, adjuvant)	Time to rebleeding (months), median [range]	Overall response rate
Kubaszewska *et al.* (52)[†]	2008	R	Polen	178	Lung cancer	Thorax	22.5 Gy/7.5 fr (weekly) (63.7%) 10 Gy/1 fr (36.3%) 8 Gy/1 fr for re-irradiation	Speiser and Spratling scale	15.6% concurrent	NA	92% (38% CR)
Nakamura *et al.* (53)	2018	P: observational	Japan	21	Breast cancer	Skin	36 Gy/12 fr (76%) 30 Gy/10 fr (10%) [30–60 Gy/10–30 fr]	Quality of life questionnaire and clinical response	14% concurrent	NA	Significant at 3 (P=0.001) and 6 (P=0.008) months
Cihoric *et al.* (54)	2012	R	Switzerland	62	Bladder (16%) Lung (15%) Endometrial (13%) Prostate (10%) Cervix (10%) Gastric (10%) Ovarian (10%) Colorectal (5%) Other (13%)	Mixed	20 Gy/5 fr [5–45 Gy/1–8 fr]	WHO bleeding grade	53% prior 3% concurrent	NA	87% (63% CR)
Sapienza *et al.* (55)	2019	R	Brazil	112	Gastrointestinal or genitourinary (38.4%) Other (61.6%)	Mixed	20 Gy/5 fr (42%) 30 Gy/10 fr (22%) 8 Gy/1 fr (19%) BED <39 Gy (91%) BED >39 Gy (9%)	Clinical response	66.1% prior 33.9% no systemic treatment	2.7	89% in total 83% at 3 months 76% at 6 months 56.4% at 12 months GI (88.6%) GU (80%) H&N (87.5%) Respiratory (92.8%) Extremities (100%) Gynecological (100%)
Kumar *et al.* (56)	2019	R	India	70	Lung (17.1%) Gynecological (17.1%) Regional lymph nodes (28.6%) H&N (10%) Bladder (10%) GI (8.6%) Breast (8.6%)	Mixed	30 Gy/10 fr (25.7%) 25 Gy/4 fr (22.8%) 20 Gy/5 fr (10%) [6.25–30 Gy/1–10 fr; weekly or daily]	Bleeding control	NA	NA	75.70%

Table 2 (*continued*)

Table 2 (*continued*)

Study	Year of publication	Retro/prospective	Country	Number of patients	Cancer etiology	Localisation	Fractionation schedule	Outcome	Systemic treatment (prior, concurrent, adjuvant)	Time to rebleeding (months), median [range]	Overall response rate
Rasool *et al.* (57)	2011	R	India	25	Bladder (48%) Cervix (16%) Lung (20%) Rectum (8%) Endometrium (4%) Schwannoma (4%)	Mixed	15 Gy/5 fr (60%) 20 Gy/5 fr (40%)	Bleeding control and Hb level	NA	NA	88% CR
Katano *et al.* (58)	2021	R	Japan	36	GU (50%) GI (19%) Skin or lymph nodes (22%) Other (8%)	Mixed	30 Gy/10 fr (42%) 20 Gy/5 fr (28%) [8–30 Gy/1–10 fr]	WHO bleeding status	NA	NA	91% (high BED) 71% (low BED)
Katano *et al.* (59)	2023	R	Japan	21	Gynecological (48%) GI (29%) Urological (14%) Other (10%)	Mixed	30 Gy/10 fr (67%) 20 Gy/5 fr (14%) 15 Gy/3 fr (5%) 8 Gy/1 fr (5%) 8 Gy/2 fr (10%	BTN at 1 month	NA	NA	90.50%
Guhlich *et al.* (60)	2023	R	Germany	68	Pelvis (59.7%) Thorax (24.7%) Abdomen (9.1%) H&N (3.9%) Skin (2.6%)	Mixed	Median 39 Gy [9–84.4 Gy/1–28 fr][‡]	Clinical response, Hb level, BTN	39.0% prior	NA	88.3
Total		R=45 (83.3%); P=9 (16.7%)	–	2,361	–	–	–	–	–	–	–

[†], use of brachytherapy; [‡], change to curative concept after achieving bleeding stop total dose was higher [in 11.7% (n=9) of patients] and excluded in the table. R, retrospective; P, prospective; GI, gastrointestinal; GU, genitourinary; H&N, head and neck; fr, fractions; BED, biological equivalent dose; CFRT, conventionally fractionated radiotherapy; SBRT, stereotactic body radiation therapy; EBRT, external beam radiotherapy; HDREB, high-dose-rate endobronchial brachytherapy; Hb, hemoglobin; BTN, blood transfusion need; CTCAE, Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; WHO, World Health Organization; NA, not assessed; CR, complete response; BT, brachytherapy.

studies regarding gastric cancer, three were prospective in nature. Saito *et al.* showed for the fractionation schedules 8 Gy/1 fr (21%), 20 Gy/5 fr (32%) with 30 Gy/10 fr (38%) a higher RR for a higher BED_{10} regimen, however it was no significant predictor (12). Sixty-nine percent of patients experienced bleeding response and 90% had a per protocol RR at 8 weeks in follow-up. In the phase 2 trial of Tey *et al.*, a 36 Gy/12 fr schedule showed a RR in 80% of patients responding to RT with a median response duration of 3.4 months (18). The prospective study of Tanaka *et al.* had an initial RR of 80.6% for bleeding on a total of 31 patients after 20 Gy/5 fr and a 100% RR for re-irradiation with additional 15 Gy/5 fr in all six patients with re-bleeding (19). All other studies reported a high overall RR varying between 70% and 95% for hypofractionated RT (20-25).

If feasible, additional chemotherapy or a higher BED led to a prolonged time to re-bleeding in the multivariate analysis of Yu *et al.* (26). Re-bleeding appeared in 35.2% of the patients at a median time of 6 months. However, it should be noted that the median OS was only 4.8 months. The small study of Yagi *et al.* found a significantly increased median survival time from 1.6 to 6.5 months if chemotherapy was introduced after palliative irradiation (P=0.001), but did not report on bleeding time (27).

For re-irradiation after re-bleeding, Kawabata *et al.* evaluated a short course of 6 Gy/3 fr followed by re-irradiation, if necessary (28). The initial treatment success was 55% and 44% and treatment success with re-irradiation was 75% and 25% after 2 and 4 weeks respectively. There is no standard treatment for gastrointestinal (GI) bleeding due to tumor invasion of unresectable pancreatic cancer. Shibuki *et al.* evaluated palliative irradiation and achieved a RR up to 70% with a low rebleeding rate (21.4%) (29). Moreover, successful hemostasis can provide the opportunity for administration of adjuvant chemotherapy, which can significantly increase OS (median 260 *vs.* 52 days).

Pelvis

Sixteen studies reported on EBRT for symptoms including bleeding for tumors in the pelvic region. Most studies were retrospective and reported on tumors of the genitourinary tract (n=7), gynecological (n=6) or rectal origin (n=1), the remaining two studies included a combination of tumor etiologies (*Table 2*). Only one study used BT for advanced prostate cancer bleeding (30).

For genitourinary malignancies, Lacarrière *et al.* and Zhang *et al.* did not find a significant difference for hemostatic effectiveness for a 30 Gy/10 fr schedule compared to 20 Gy/5 fr (31,32). However, the relapse rate was lower in the latter group (46% *vs.* 21%) (31). Ogita *et al.* differentiated on BED with 26% of patients receiving 30 Gy/10 fr (BED_{10} 39 Gy), 23% 20 Gy/5 fr (BED_{10} 28 Gy) and 21% 36 Gy/12 fr (BED_{10} 46.8 Gy) for hematuria, mostly due to bladder (41.5%) and prostate cancer (30.2%) (33). In the multivariate analysis BED_{10} ≥36 Gy was statistically significant for prolonged hematuria control (8.4 *vs.* 0.7 months, P=0.02).

Dirix *et al.* assessed a high hematuria free survival of 80% for mean follow-up of 9.4 months for weekly bladder irradiation in 34.5 Gy/6 fr (34). This regimen was associated with mild toxicity with only 9% severe acute toxicity (grade 3). Coraggio *et al.* reported a highly efficient hemostatic control for acute and mid-term follow-up (6 months) up to 100% and 67% respectively with no significant difference (P=0.48 and P=0.45 respectively) between a continuous regimen of 3–6 Gy/fr to a total dose of 18–30 Gy (n=14) and a "discontinuous" schedule of 23 Gy in 4 fr [6.5 Gy/fr on days 1 and 3, followed by 5 Gy/fr on days 15 and 17 (n=12)] (35).

Specific for bladder cancer Tey *et al.* retrospectively found a 61% RR in patients received low BED_{10} (<36 Gy) compared to 77% in the high (≥36 Gy) group; however, 50% of the low BED had recurrence of hematuria compared to only 13% of high BED regimen (P=0.01) (36).

The study of Thurairaja *et al.* used 24 Gy in high-dose rate (HDR) intra-urethral BT in advanced prostate cancer with a RR for macroscopic hematuria of 83% at the 6-month follow-up (30). Two out of four patients with persistent macroscopic hematuria received a repeat course intraurethral HDR-BT with the same dosage. Both patients did not show response and had persistent hematuria.

For malignancies of gynecological origin, Butala *et al.* found a similar time to hemostasis and the overall bleeding control for short course regimen (≤5 fr, median BED_{10} 28 Gy) compared to protracted conventional regimen (8–50.4 Gy in 1–28 fr) (37). Yan *et al.* evaluated irradiation regimen of a total dose of 24 Gy with 3 equal fractions with intervals of 7 days between fractions 1 and 2, and 14 days between fractions 2 and 3 (0-7-21 regimen) with a RR of 92% and a complete response in 62% of patients (38).

In ovarian cancer a complete response for bleeding varied between 80% and 88% with dose fractionation schemes ranging 5 Gy/1 fr to 53 Gy/28 fr, the majority hypofractionated regimen with 30 Gy/10 fr as most common (39,40). For cervical cancer the median fractionation schedule of 25 Gy/5 fr was assessed to have a high overall response (93.8%), in patients with predominantly vaginal bleeding (41). Mishra *et al.* evaluated monthly palliative RT at 30 Gy/3 fr for vaginal bleeding were complete response increased from 31% after one fraction to 100% at the end of the third fraction (42).

Chia *et al.* found a high RR of 86.7% in patients with primary rectal cancer who presented with bleeding alone (n=67) or in combination with pain or obstruction (n=16) (43). Regimens varied between 18–54 Gy in 6–30 fr, with the 30 Gy/10 fr regimen most prevalent.

Two studies assessed the hemostatic effect of irradiation for heterogeneous pelvic malignancies and were prospective in nature. The phase 1 trial of Caravatta *et al.* investigated twice daily short-accelerated re-irradiation of 14–18 Gy/4 fr in 2 consecutive days in the palliative setting with an overall symptom remission of 88.9% (44). Farina *et al.* had a 96% overall RR for their SHARON protocol of 18 Gy/4 fr, twice daily in a phase 2 study (45).

Lung

For symptomatic malignant lung lesions, from either primary lung cancer or endobronchial metastatic lesions originating from extrapulmonary disease, we found one study on EBRT and six on BT. Three of the BT studies were prospective.

Regarding EBRT, Fleming *et al.* evaluated stereotactic body radiation therapy (SBRT) (≥5 Gy/fr) over conventionally fractionated radiotherapy (CFRT) (≤4 Gy/fr) (46). In general, there was a high RR to hemoptysis (86.2%), but the univariate analysis showed a lower durable symptom relief in the high BED CFRT group (BED_{10} >39 Gy).

For high-dose-rate endobronchial BT (HDREB) the prospective study of de Aquino Gorayeb *et al.* saw resolution of hemoptysis in all patients with malignant airway obstruction treated with a 22.5 Gy/3 fr regimen HDREB, with or without EBRT (60 Gy/30 fr or 30 Gy/10 fr) (47). The phase 2 study of Mallick *et al.* compared EBRT with two sessions of HDR-BT of 8 Gy or one fraction of 10 Gy to HDR-BT alone in a single fraction of 15 Gy in non-small cell lung cancer (48). The overall symptomatic RR did not show a significant difference between the study arms; however, hemoptysis palliation was significantly shorter in the HDR-BT only group (P<0.01). Their retrospective review reported symptomatic RR of 97% for hemostasis (49). The study of Siddiqui *et al.* retrospectively reviewed 14 Gy/2 fr of weekly HDREB for 58 patients with endobronchial malignancies, including patients with previous EBRT (52%) which was associated with significant increase in adverse events (57% *vs.* 25%, P=0.018) (50). The RR for hemoptysis was 88% compared to dyspnea and cough (72% and 48.6%, respectively) and the median progression free survival after symptom palliation was 6.5 months. Donovan *et al.* prospectively reviewed the application of HDREB endobronchial metastases of extrapulmonary malignancies (51). A median dose of 21 Gy/2–3 fr improved hemoptysis in 76% of cases, but only 11.76% had a complete response.

The largest study in our review (n=270) evaluated retrospectively HDREB for symptom control in previously irradiated patients (52). Hemoptysis was present in 66% of patients and the RR and complete response (92% and 38%, respectively), were higher compared to RR for cough, dyspnea and pneumonia (77%, 76% and 82%, respectively).

Breast

We found one study on hemostasis of the breast: Nakamura *et al.* prospectively evaluated median dose 36 Gy/12 fr to significantly reduce bleeding due to breast cancer related skin invasion at 3 months (P=0.001) and at 6 months (P=0.009) (53).

Mixed

We found seven retrospective studies on hemostatic RT for a variety of different cancer etiologies in different parts of the body (thoracic, abdominal, pelvic, etc.).

Cihoric *et al.* suggested better response to hemostatic RT in the lung (100%), uterovaginal (95%), and upper GI lesions (90%) compared to bladder involved lesions (54). Sapienza *et al.* also found lower bleeding control in urinary tract of 80% compared to 88.6% to 100% in malignancies originating from elsewhere (55). For the three most occurring regimen 20 Gy/5 fr, 30 Gy/10 fr and 8 Gy/1 fr, no difference was found for overall bleeding control (55,56). Neither 15 Gy/3 fr showed any difference (57). Overall RR varied from 75.7% to 89% and remained up to 56% at 12 months (55-57). Number of fractions and BED_{10} above 39 Gy did not influence bleeding control, nor re-bleeding rate.

The study of Katano *et al.* from 2021 examined a heterogeneous population for a high and low BED arm treated with mostly 30 Gy/10 fr and 20 Gy/5 fr respectively (58). The high BED group had a 91% improvement in World Health Organization (WHO) score compared to a 71% improvement in WHO score for the low BED group with no statistically significant difference in RR (P=0.20). In 2023 the group revealed a significant improvement in transfusion need after palliative irradiation (59). The multivariate analysis in the retrospective study of Guhlich *et al.* showed a significantly improved clinical bleeding response from 88.3% towards 95% if patients completed the intended fractionations schedule (60). Reasons of interruption of treatment were early stop due to patient deterioration, patients' decision or complications before or after bleeding control and patient death.

Discussion

Palliative RT has a high rate of symptom relief for patients with cancer-related bleeding. However, there are no clear guidelines to determine the optimal timing of RT, total dose, dose fractionation and whether or not to use concomitant treatment for the optimal outcome.

Prospective trials focusing on hemostatic RT specifically are sparce. During our search we found the prospective trial of Lozano Galan, that has recently closed. However, the results of this trial are not yet available (61). In this trial, patients with rectal cancer who are ineligible for surgery are treated with palliative RT with a total dose of 39 Gy/13 fr in 17 days. The endpoint of this trial is symptomatic response after treatment, with one being the effect of RT on bleeding according to the CTCAEv4.0 scale. A phase III prospective study of Tey *et al.* was planned according to the phase II trial study published in 2019, but was not yet found in literature (18).

The most of the available data in literature on hemostatic RT is retrospective. We believe that a proper review of the data is necessary to provide some guidance for clinical practice. We believe that our review provides the most up-to date and a clear overview of relevant data on hemostatic RT currently available.

We believe three recently published reviews have some issues that make it difficult to determine the exact value of their findings. They all reported high effectiveness for hypofractionated hemostatic RT for diverse tumor etiologies and total dosage but also concluded more prospective research was necessary (2-4). The review of Johnstone *et al.* from 2018 discussed several systemic and topical therapeutical options, including RT, for bleeding control (3). They highlighted the importance of patient estimated life expectancy and feasibility to choose an appropriate treatment. However, they focused their review on discussing high dose, short irradiation treatment with a palliative intention from mostly retrospective studies without a specific focus on bleeding. Moreover, the methodology for their search was not properly described (3). The review, by Shah *et al.* from 2021, also does not provide an in-depth description of their methodology regarding search terms, searched databases, the time-period researched and the inclusion and exclusion criteria (4). This review included only six articles, all retrospective in nature and one being a case report. The most recent review of Song *et al.* was published in 2023 and included 13 prospective and 45 retrospective studies (2). Similarly to our review, they looked at efficiency of hemostatic RT for different subsites, which appears to be important for decision-making in clinical practice. However, despite being published in 2023, their search only included studies published up to 2017, thus missing the most recent data available.

Our review shows that hemostatic irradiation is safe for both high and low BED regimens, however without uniformity in different fractionation schedules. Daily irradiation was used in the majority of the studies; however, weekly high-dose fractionation schedules are proven to be equally effective in the palliative setting for bladder cancer.

This review unfortunately doesn't highlight an optimal treatment schedule. However, BED may be indicative for optimal bleeding control and could be used during clinical decision making for some tumor etiologies. A widely accepted palliative fractionation schedule is 30 Gy/10 fr, which corresponds to a BED of 39 Gy at a α/β of 10. However optimal BED cut-offs probably vary for different tumor etiologies and associated symptoms. For gastric cancer, no differences were seen between high-dose *vs.* low-dose regimens for symptom relief at the cut off BED_{10} 39 Gy; however, bleeding response in gastric cancer is inferior for fractionation schedules BED_{10} <30 Gy (62,63). For unresectable pancreatic cancer, higher radiation doses tend towards better RRs which could even improve OS if additional chemotherapy is feasible (29).

In the treatment of bladder cancer related hematuria, a higher BED_{10} is not statistically significant associated with a better RR (64). However, bladder-associated hematuria appears to be more radioresistant for bleeding control; therefore, a BED_{10} >36 Gy is generally recommended to reduce recurrence rate (54,55). Patients with poor performance status and with hemorrhage originating from the pelvic region may even benefit from ultra-hypofractionation schedules of twice daily irradiation for 2 consecutive days with generally good palliative RRs (44,45). Alternatives such as weekly high-dose fractions, used in bladder cancer or monthly irradiation for cervical cancer has also been proven to be efficient (34,42,65). These hypofractionation schedules with an increased overall treatment time is associated with higher BED regimen and allows more time for recovery from acute toxicity (66). The low alpha-beta ratio of bladder cancer cells according to *in vitro* data of Kang *et al.* could support the use of high-dose hypofractionated RT as these malignant cells are possibly more resistant to RT (67). In bleeding response for hemoptysis in lung cancer, there is no indication for high-dose regimens exceeding BED_{10} 30 Gy (68). However, for patients needing palliative thoracic RT due to additional symptoms of obstruction and/or dysphagia, higher BED_{10} 35 Gy is recommended, weighed against patient performance status and risk of increased toxicity (69).

The majority of studies on BT for hemostasis focused on patients suffering from hemoptysis. The antineoplastic effect of BT causes radiation induced thrombosis and endothelial damage of the ruptured neovascular tumor surface (70). HDREB provides a rapid dose fall off and dose distribution with limited dose on surrounding organs and can safely offer advantages for re-irradiation. In the setting of re-irradiation and no extensive tumor localization, HDREB is highly efficient for local symptom control for primary lung tumors and pulmonary metastasis (47-51). Irradiation dose can be escalated based on the adjacent organs at risk. If airway obstruction with external pressure by the tumor is present, combination with EBRT might be necessary (52). However, tumor size, rather than BED, is related to treatment success rate and a better clinical result is seen for hemoptysis compared to dyspnea or cough (46,52).

In general, fractionation schemes of more than five fractions were significantly related to an increased chance of treatment interruption (22.2% *vs.* 5.3%, P=0.02) in univariate and multivariate analyses (54,55). Although higher BED fractionation schedules tended towards higher efficiency in univariate analysis, multivariate analysis remain important. In the multivariate analysis, efficiency of treatment may be affected due to poor patient performance score (leading to early treatment interruption), tumor localization and prior irradiation (both limiting dose prescription for nearby organs at risk), addition of chemotherapy (increased toxicity), etc. The heterogeneous patient population and a variety of tumor etiologies and localizations require an analysis between the multiple variables and their complex relationship to improve a more accurate understanding of the benefit of the used fractionation schedules. However, multivariate analysis of retrospective trials needs to be reviewed with caution, as imputation may be needed to compensate for missing data (71). Additionally, the statistical modeling outputs are not always easy to interpret by non-statisticians.

Because not many retrospective studies could significantly prove any benefit for higher BED regimen with more prolonged regimen, treating radiation oncologists should prefer short-course regimens. The choice for lower BED regimen for patients with a higher PPI (and lower prognosis) are more feasible and is supported with practical arguments for palliative care (logistics, cost effectiveness, patient/family burden) (72,73). The multicenter prospective observational study JROSG 17-3 on palliative RT for gastric cancer related bleeding showed a high predictive value of the PPI for short-term mortality (<2 months) (74). Additionally, attributed to the high bleeding RR, they found a high response on anemia-related dyspnea for hemostatic irradiation, but only an improvement in fatigue in the subgroup of patients treated with single-fraction irradiation (8 Gy/1 fr; BED_{10} <14.4 Gy) compared to multiple-fraction RT (12,74,75).

The clinician's evaluation of the patient's general status is important to assess the feasibility of radiation treatment. An incomplete irradiation course, due to patient deterioration (related to disease progression, patient QoL preferences or comorbidities), leads to a drop in treatment efficiency of an intended high BED regimen below the RR of moderately low BED regimen (9). A short treatment duration is preferred over high BED regimen and if no short fractionation schedule is feasible, other hemostatic interventions might be preferred.

A trend toward hypofractionation is accompanied by studies focusing on re-irradiation (19,28). The benefit of re-irradiation and the improved OS is mostly based on selection bias. For example, patients had to be willing to undergo a second treatment course and had to require a sufficient general condition and life expectancy had to be over 1 month.

For better clinical outcomes, concurrent chemotherapy with palliative RT has been used in several studies (*Table 2*). Although the RR of RT with chemotherapy was higher, it is more burdensome and should be questioned in the terminal stage of the disease for patients with low performance status and general condition. Prior chemotherapeutic regimens to RT do not appear to cause additional significant toxicity (39).

Alternative hemostatic interventions other than RT should be evaluated for treatment decision to select the appropriate treatment modality for each patient based on each patient's general condition, prognosis, surgical tolerance, complications, and bleeding site.

We limited our search to the PubMed database and included only studies published from the last 20 years. However, compared to a recent review on hemostatic review including studies from 1947 until 2017 form three different databases, only three additional studies were included if they met our exclusion criteria (2). Additionally, we included 27 studies published in the last 5 years, from 2018 until December 2023 who also referred to the oldest studies before 2003. Other limitations are the lack of prospective studies, small sample size studies and the heterogeneity of fractionations schedules. Long protracted fractionation schedules with appearance of a curative design were excluded for this review. The heterogeneity of RR based on different tumor etiologies, treatment localization and RT doses make it difficult to identify associations of outcome with specific tumor or treatment factors. Additionally, the RR, was not uniformly assessed. Clinical bleeding control was often subjective or heterogeneously assessed with different score indices such as the WHO bleeding score, the PPI or the Speiser and Spratling score, the latter in studies with HDREB for hemoptysis (47). Hemoglobin measurement can be a good parameter for monitoring bleeding response. Hemoglobin is essential to maintain tissue oxygenation which is compromised during bleeding as a result of a decreased blood flow leading to dyspnea, fatigue and feelings of being distressed. According to the palliative care-oriented practice review of Neoh *et al.*, investigation of anemia is preferred with a rather restrictive approach to the need for blood transfusions (76). Red blood cell transfusion may provide subjective relief of clinical symptoms, but the overall benefit remains unclear. Nevertheless, it could be a relevant factor to objectively evaluate the overall RR for hemostatic treatment (77). Additional examinations, such as computed tomography-based examination or endoscopic bleeding evaluation would cause an increased burden on patients and have no or limited place in the palliative setting.

Several studies did not solely focus on hemostasis, but included other symptoms accompanied with tumoral spreading into adjacent tissue. In general, it seems that bleeding responds better to RT compared to other symptoms such as pain, discomfort, dyspnea etc. In all studies that reported symptom relief, bleeding showed the highest RR compared to symptom relief from other tumor related discomforts (compression, pain, etc.). Unfortunately, based on the found evidence, no clear recommendations for hemostasis alone can be given. All palliative hypofractionated schedules, both EBRT, included stereotactic RT, and BT could be of use.

Conclusions

Hypofractionated RT is an effective treatment in palliative care for oncology patients with low toxicity rates. Due to the current lack of prospective data there seems to be a wide variety in clinical practice in treatment choice for dose and fractionation regimens based on the radiation oncologist's experience, patient's performance status and additional symptoms besides bleeding. This review supports the use of relatively low dosed hypofractionated regimens, but prospective studies are needed to objectively evaluate RR, as certain etiologies may require a minimal irradiation dose for an optimal response.

Hemostatic RT, both by EBRT and BT, appears to be a safe and effective palliative treatment that clinically and statistically significantly reduces bleeding in cancer patients. The available literature is limited regarding prospective data and uniform evaluation of hemostatic RT, including fractionation schedules. The BED seems to be indicative for a better RR for specific indications such as more radioresistant tumor etiologies. Current evidence suggests that treatment decisions regarding hemostatic RT should be tailored according to the patients' condition and other associated symptoms. More (prospective) research focusing on hemostasis is necessary to develop a clear guideline.

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Footnote

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