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Original Research Article

Patterns of practice in palliative radiotherapy for bleeding tumours in the Netherlands; a survey study among radiation oncologists

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ABSTRACT

Background and purpose: Palliative radiotherapy (RT) is one of the treatment options for bleeding tumours; a frequent symptom in patients with advanced cancer. The optimal RT schedule is however unclear. This study explores the current pattern of practice of palliative RT for bleeding tumours in the Netherlands.

Materials and methods: An internet-based questionnaire, including respondent characteristics, factors influencing the choice of RT schedules and five patient case scenarios, was sent to all members of the Dutch Society for Radiation Oncology. Descriptive statistics were used to evaluate the results.

Results: The response rate was 125/374 (34%); representing 20 out of 21 Dutch RT departments. Most reported influencing factors were performance status, prognosis, patients' comfort and patients' choice. Most preferred RT schedules were 1 × 8 Gy for hematemesis, 1 × 8 Gy and 5 × 4 Gy for haemoptysis, 5 × 4 Gy for haematuria, 5 × 5 Gy for rectal bleeding, 1 × 8 Gy, 5 × 4 Gy and 10-13 × 3 Gy for vaginal bleeding.

Conclusions: The current patterns of practice in the Netherlands for bleeding tumours varied considerably. Most often a single fraction is chosen (35% of all cases), followed by a five-fraction schedule (30% of all cases). The choice of an RT schedule is mainly influenced by patient related factors.

1. Introduction

Bleeding occurs in approximately 6–10% of patients with (locally) advanced cancer [1]. Bleeding tumours can present in several ways, including hematemesis, haemoptysis, haematuria, rectal bleeding or vaginal bleeding. It can have a significant impact on the quality of life of both patients and their caregivers, causing anxiety and distress and may result in hospitalization and/or the need for blood transfusions. Depending on the anatomical localization, there are several treatment options to manage bleeding, such as stopping coagulants, pressure bandages, surgery or embolization [1].

There is substantial evidence that palliative radiotherapy (RT) is effective in the management of bleeding, with reported treatment response (i.e. that bleeding would stop or diminish) varying from 45% to 100% [2–25]. It is, however, not clear which RT schedule, with regard to fractionation and total dose, is most 'optimal' (with as less fractions and less toxicity for the patient and as much as possible effect on symptom control) to manage bleeding. The presence of complaints other than bleeding (e.g. pain or obstruction) and the aim to reduce tumour volume can influence the chosen fractionation and total dose. Therefore, RT schedules described in literature vary considerably between studies (total dose ranged from 5 to 76 Gray {Gy}, number of fractions ranged from 1 to 39), consisting of only a few randomized controlled trials (RCTs) that compared different RT schedules, mainly with limited numbers of patients [2–13,16–18,20,22,23]. Table 1 summarizes the main studies on palliative radiotherapy in the management of bleeding using external beam radiotherapy (randomized and retrospective studies including information with regard to bleeding of at least 30 patients) that provide information with regard to fractionation schemes used, the bleeding control rate and/or duration

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Table 1
Review of literature.

Author	Year	n	study type	symptoms	RT dose (Gy)/ fractions	Bleeding control rate	time to response	Duration of response
MRC Lung Cancer working party [2]	1991	369	RCT	Haemoptysis	17/2 vs 30/10 and 27/6	81% vs 86%	N/A	4.5 months for both groups
MRC Lung Cancer working party [3]	1992	235	RCT	Haemoptysis	17/2 vs 10/1	75% vs 72%	N/A	2.4 months for both groups
Asakura et al [4]	2011	30	Retrospective	Hematemesis	30/10	73%	N/A	3.3 months
Chaw et al [5]	2014	52	Review	Hematemesis	8/1 and 20/5	50%	<4 weeks	N/A
Lee [6]	2017	42	Retrospective	Hematemesis	Various	69%	2 weeks	3.4 months
Murakami et al [7]	2008	54	Review	Hematemesis and rectal bleeding	Various	Haematemesis: 54%, rectal bleeding: 64%	N/A	haematemesis: 4.6 months rectal bleeding: 10 months
Cameron et al [8]	2014	1759	Review	Rectal bleeding	Various	81%	N/A	N/A
Srinivasan et al [9]	1994	41	Retrospective	Hematuria	17/2 vs 45/12	59% (17/2) and 16% (45/12)	N/A	N/A
Duchesne et al [10]	2000	272	RCT	Hematuria	35/10 vs 21/3	89% vs 86%	50% <2 weeks	9 months
Lacarriere et al [11]	2013	32	Retrospective	Hematuria	30/10 and 20/5	54% (30/10) and 79% (20/5)	<2 weeks	3.6 months
Cameron et al [12]	2014	471	Review	Hematuria	Various	73%	N/A	N/A
Dirix [13]	2016	44	Retrospective	Hematuria	34.5/6	89%		13 months
Onsrud et al [14]	2001	46	Retrospective	Vaginal bleeding	10/1–30/3	88%	N/A	N/A
Mishra et al [15]	2005	69	Retrospective	Vaginal bleeding	10/1–30/3	100%	N/A	N/A
van Lonkhuijzen et al [16]	2011	596	Review	Vaginal bleeding	Various	45–100%	N/A	N/A
Cihoric [17]	2012	62	Retrospective	Various	Various	87%	N/A	N/A
Sapienza et al [18]	2018	112	Retrospective	Various	Various	89%	N/A	at 3 months: 83% at 1 year 56%

Year = year of publication, n = number of patients analyzed, RCT = randomized controlled trial, N/A = not analyzed.

of bleeding control. In general, reviews for hematemesis, rectal bleeding and vaginal bleeding show response rates between 50% and 90% [6–8,16]. For haemoptysis and haematuria limited RCT data are available, showing no difference in treatment response rates: for haemoptysis response rates vary between 54% and 86% for different RT schedules (range 10–60 Gy in 1–39 fractions) [2–3,22]. For haematuria no difference in treatment response was observed comparing 10 × 3.5 Gy and 3 × 7 Gy (response rate at three months 65% and 63%, respectively) [10]. The interval between start of radiotherapy and achieving hemostasis is only a couple of days [26].

In the Netherlands, there is fair agreement on the most optimal treatment for other palliative indications, e.g. for painful bone metastases a single fraction of 8 Gy is generally accepted [27,28]. However, no consensus exists on the palliative RT schedules used for bleeding tumours.

The primary aim of this study is to examine the current patterns of practice of palliative RT for bleeding tumours (i.e. hematemesis, haemoptysis, haematuria, rectal bleeding and vaginal bleeding) in the Netherlands. Because of less frequent occurrence in daily practice, other bleeding tumors (e.g. bleeding brain metastases or skin lesions) are not subject of this study. Secondly, this study aims to examine the considerations for deciding on palliative RT treatment, for choosing a specific RT schedule in hematemesis, haemoptysis, haematuria, rectal bleeding and vaginal bleeding, and the expected treatment response.

2. Materials and methods

2.1. Participants, questionnaire construction and distribution

An internet-based questionnaire (in Dutch), using SurveyWorld (Syncforce ©, Eindhoven, The Netherlands), was developed to explore the patterns of practice in palliative RT for bleeding tumours (hematemesis, haemoptysis, haematuria, rectal bleeding and vaginal bleeding) in the Netherlands. This questionnaire was filled in anonymously and included general questions about the respondents' characteristics, factors influencing the choice of RT schedules, and expected effectiveness of RT (Appendix A Supplementary data). In addition, five patient cases including eight clinical scenarios were developed to study individual treatment preferences. Given the length of the questionnaire, we have limited the clinical cases to the most frequent types of bleeding. The questionnaire was designed using the Dillman method [29–31]. The concept questionnaire was reviewed by two independent radiation oncologists (ROs) and subsequently tested by eight additional ROs to establish ease of completion, completion time and relevance. Feedback was asked in person and by e-mail. All these ROs were members of the Dutch Platform for Palliation and Radiotherapy, a nationwide platform consisting of all Dutch Radiation Oncology departments. Subsequently, the questionnaire (Appendix) was distributed among all members (N = 374, 275 ROs and 99 residents) of the Dutch Society of Radiation Oncology (NVRO, Nederlandse Vereniging voor Radiotherapie en Oncologie). A reminder was sent after two weeks. The questionnaire was closed after five weeks. No reimbursement was offered.

2.2. Statistical analysis

Data obtained from all respondents were analysed using descriptive statistics for categorical variables. Results are displayed as frequency tables, both for influencing factors and preferred RT schedules for all five patient cases.

The study was reviewed by the internal review board of MAASTRO clinic. No ethics board approval was required for this study.

3. Results

3.1. Respondents

A total of 125 members (33.4%) of the NVRO responded: 103 ROs (37.5%) and 22 residents (22.2%). Responses were obtained from 20 out of 21 RT departments with a median of five responders per department (range 1–19). Of the 103 ROs, 72 (70%) works five or more years in clinical oncology practice. A median of 5–10 patients with bleeding tumours are seen per respondent on a yearly base, with an equal distribution between all types of bleeding tumours. Fifty-eight respondents (46%) mentioned palliative RT as one of their specialties in RT.

3.2. Influencing factors

Fifteen factors influencing the choice of an RT schedule were analysed. Results are shown in Table 2. Performance status (PS), prognosis, patients' comfort and patients' choice were mostly reported as influencing factors. Tumour volume and primary tumour were mentioned less often. Factors that did not contribute to preferred schedules were: expected late toxicity, time between registration and RT, and the availability of linear accelerators. An RT schedule of less than ten fractions was most often preferred when patient's life expectancy was considered less than six months. Ten or more fractions were preferred if the patients' life expectancy was considered more than six months, no distant metastases were identified and a long-term response was aimed to achieve.

3.3. Treatment response of RT

Respondents were asked about the expected effectiveness of RT considering treatment response, time to treatment response and duration of treatment response. Only a limited number of RO's answered these questions (20–37% of the 125 respondents). Most respondents (74%, n = 26/35) mentioned an expected treatment response of 70–80%. Four respondents mentioned a treatment response between 60% and 70%, only one expected a treatment response of <60%. All respondents (n = 26) expected diminished bleeding within eight weeks after RT, eleven of these within four weeks. There was a wide range in expected duration of response, mainly several weeks to months. A few respondents (7%, n = 3/46) expected that the response could last for more than one year. Some of the responders noted that the expected treatment response might be influenced by RT schedule, primary tumour, location of RT, extent of disease and systemic treatment.

3.4. Patient cases

The questionnaire contained five patient cases with a total of eight scenarios. Case 1 until 3 are divided in two clinical scenarios each. The results of the all scenarios are described below and summarized in Fig. 1a–h for all eight clinical scenarios of bleeding separately.

Hematemesis-1: Eighty year old man, PS 1, ulcerating oesophagus carcinoma (no obstruction), liver metastases, hematemesis for three days, patient's wishes were no chemotherapy but stop hematemesis, no previous RT.

RT was the preferred treatment in 98% of respondents. The preferred treatment options were: 84% external beam RT, 14% brachytherapy and in 2% RT was not otherwise specified. Most often 1 × 8 Gy (37%) (Fig. 1a) was chosen. Some respondents mentioned a second fraction of 8 Gy when the effect of the first fraction is unsatisfactory.

Hematemesis-2: The primary tumour in this case scenario changed into a carcinoma of the stomach. In this scenario 97% opted for RT. Again, 1 × 8 Gy (34%) (Fig. 1b) was the most common schedule chosen.

Hemoptysis-1: Seventy year old woman, PS 2, non-small cell lung cancer (NSCLC) and chronic obstructive pulmonary disease. Haemoptysis for one month caused by a tumour in the main bronchus. Stereotactic RT four years ago in the right upper lobe (T1N0). Since three months loco-regional recurrence, adrenal and bone metastases. Patient suffers from haemoptysis and fatigue (Hemoglobin (Hb) 5.2 mmol/l).

RT was preferred by 99% of the respondents. All respondents opted for external beam RT. Most often preferred schedules were 1 × 8 Gy (31%) and 5 × 4 Gy (30%) (Fig. 1c). Some respondents would consider a second fraction of 8 Gy in case of insufficient response after the initial fraction.

Hemoptysis-2: In this case scenario, the patient had a T1N2 NSCLC in the right upper lobe with positive lymph nodes in station 4 right and 7, treated with concurrent chemo radiation to a total dose of 66 Gy, four years ago.

In this scenario 97% of the respondents preferred RT, mainly 1 × 8 Gy (35%) (Fig. 1d). Several respondents added that the preferred scheme was dependent on the previous and actual dose in the organs at risk (*e.g.* spinal cord, total lung dose).

Table 2
Influencing factors.

Influencing factors	Very important		Important		Reasonably important		Less important		Not important	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Performance status	83	(66)	32	(26)	3	(2)	4	(30	3	(2)
Prognosis	56	(45)	53	(42)	8	(6)	5	(4)	2	(2)
Patient's comfort	56	(45)	51	(41)	13	(10)	1	(1)	3	(2)
Patient's choice	34	(27)	50	(40)	25	(20)	12	(10)	3	(2)
Re(irradiation (same volume)	30	(24)	53	(42)	21	(17)	16	(13)	3	(2)
Stable vs non(stable Hb	22	(18)	59	(47)	17	(14)	16	(13)	10	(8)
Additional symptoms (e.g. pain, obstruction)	13	(10)	64	(51)	31	(25)	13	(10)	3	(2)
Multiple metastases	12	(10)	54	(43)	28	(22)	26	(21)	4	(3)
Time between registration and radiotherapy	10	(8)	45	(36)	12	(10)	21	(17)	36	(29)
Tumor volume	8	(6)	47	(38)	36	(29)	27	(22)	6	(5)
Department policy	8	(6)	59	(47)	40	(32)	15	(12)	2	(2)
Guidelines	8	(6)	55	(44)	36	(29)	19	(15)	4	(3)
Age	7	(6)	32	(26)	30	(24)	33	(26)	21	(17)
Late toxicity	4	(3)	13	(10)	16	(13)	60	(48)	29	(23)
Availability linear accelerators	2	(2)	13	(10	11	(9)	31	(25)	67	(54)

n = absolute number of respondents, % = the number of respondents in percentages. This table shows fifteen influencing factors and its importance for the choice of a fractionation scheme for palliative RT in bleeding tumors (hematemesis, hemoptysis, hematuria, rectal bleeding and vaginal bleeding).

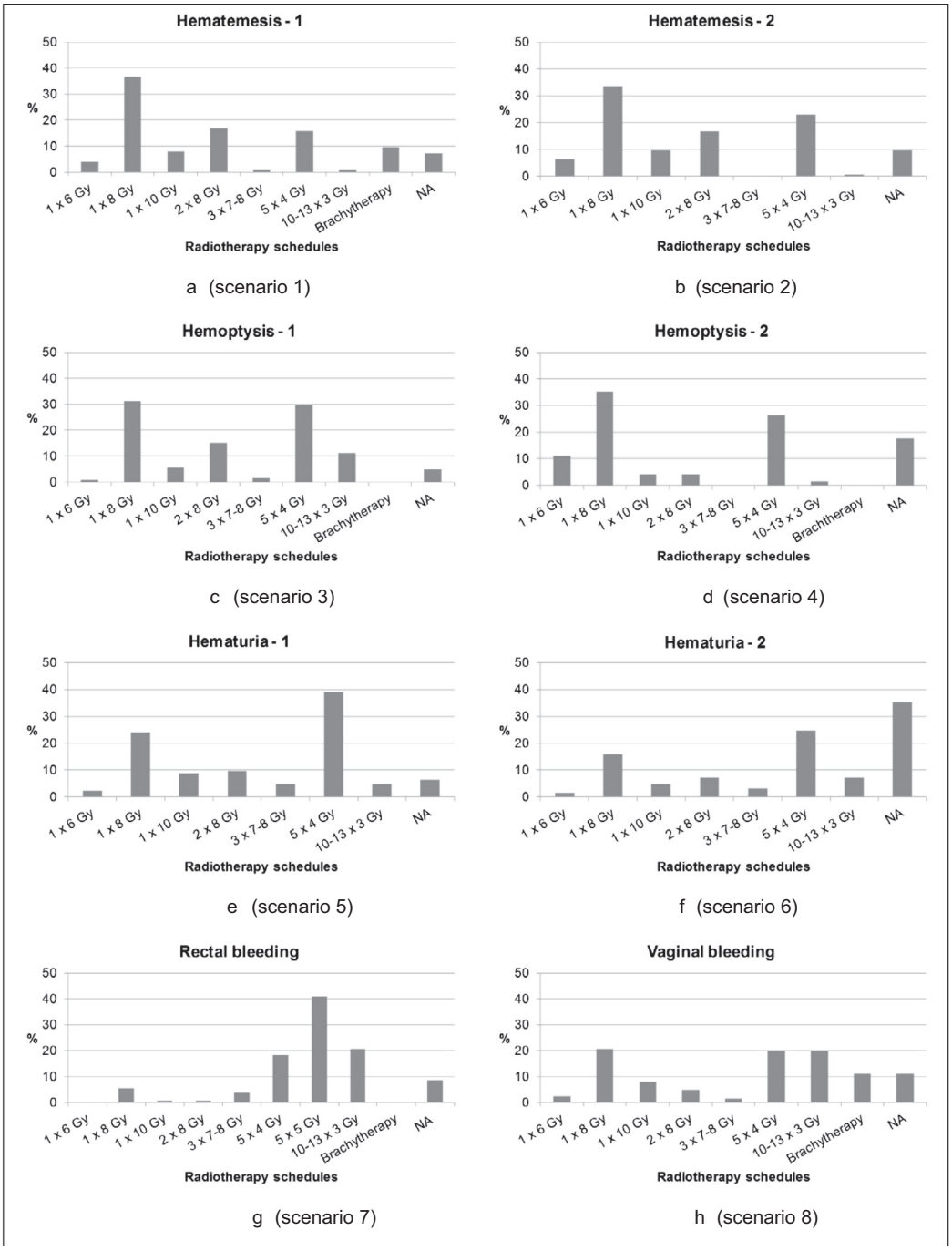

Fig. 1. (a–h) Preferred RT schedules in patient cases (8 clinical scenarios). a = chosen RT schedules for hematemesis-1, b = chosen RT schedules for hematemesis-2, c = chosen RT schedules for hemoptysis-1, d = chosen RT schedules for hemoptysis-2, e = chosen RT schedules for hematuria-1, f = chosen RT schedules for hematuria-2, g = chosen RT schedules for rectal bleeding, h = chosen RT schedules for vaginal bleeding.

Hematuria-1: Sixty-three year old man, PS 1, bladder carcinoma with metastases, urine with blood clots and fatigue. Hb 4.8 mmol/l and blood transfusion is performed. Hb not stable and decreases again.

Almost all respondents (99%) opted for RT, most often 5 × 4 Gy (39%) (Fig. 1e).

Hematuria-2: The non-stable Hb in this case scenario changed into a stable Hb after one blood transfusion.

Because of the stable Hb, 33% (n = 41) of the respondents indicated not to irradiate, while 66% (n = 82) stated that a stable Hb had no influence on the decision to irradiate (1% non-responders). An RT schedule of 5 × 4 Gy (25%) (Fig. 1f) was preferred most often.

Rectal bleeding: Seventy year old man, PS 1, extensive cardiac history. Constipation and rectal bleeding caused by rectal carcinoma (invasion in bladder and prostate), six liver metastases, three lung metastases, positive lymph nodes para-aortic. Not eligible for palliative chemotherapy.

RT is preferred by 98% of the respondents, mainly 5 × 5 Gy (41%) (Fig. 1g). A reason to choose a more fractionated RT schedule is the lack of other treatment options besides RT and higher expected local control with a higher dose.

Vaginal bleeding: Fifty-five year old woman, PS 1, history of cervical carcinoma stage IB1 for which operative treatment. Three years later vaginal bleeding, no other symptoms, caused by tumour recurrence in the vaginal vault. Extensive lymphatic and lung metastases.

Most respondents (98%) preferred RT. The majority of respondents (81%) opted for external beam RT, while 16% would prefer brachytherapy and in three respondents RT was not otherwise specified. This specific case showed more variation in preferred RT schedules: 1 × 8 Gy (21%), 5 × 4 Gy (20%) and 10-13 × 3 Gy (20%) (Fig. 1h).

4. Discussion

Despite the lack of guidelines and comparative effectiveness of RT schedules used to achieve haemostatic response, 1 × 8 Gy, 2 × 8 Gy, 5 × 4 Gy, 5 × 5 Gy and 10-13 × 3 Gy were consistently preferred for all types of bleeding tumours in the Netherlands. This shows a wide range which is also observed in the literature. RT schedules mentioned in the literature include 1-3 × 6-10 Gy, 5 × 4-5 Gy, 10 × 3-4 Gy, 15 × 3 Gy and 16-30 × 2 Gy with treatment responses varying from 45% to 100% [2–12,16,20,22,23] From the respondents which answered the open-ended questions in this study, most expected a treatment response of 70–80%. Only a few respondents expected that the response could have a prolonged effect over a year.

Most responders stated the duration of hemostasis could last several months and could vary significantly between patients and was expected to be influenced by several factors like RT schedule, primary tumour, location of RT, extent of disease and systemic treatment.

Performance status, prognosis, patients' comfort and patients' choice were mentioned as the most influencing factors for a preferred RT schedule. Consistently, it was also observed in the literature that PS most strongly influenced the preferred fractionation scheme [5,9,11]. However, other considerations for deciding on treatment or additional influencing factors for deciding on an specific RT schedule are lacking in the published papers. Overall, available studies mainly consist of small patient groups, including many retrospective studies and only a few RCTs.

To our knowledge, this is one of the first study on patterns of practice in bleeding tumours in general. Kosugi *et al.* conducted a survey in Japan focusing on hemostatic irradiation in gastrointestinal and genitourinary tumours and revealed that the number of patients treated was rather small and that the fractionation regimens varied markedly among the respondents, being 30 Gy in 10 fractions one of the most frequently used regimens [32].

Applying a high single doses seems logical. Lacarrière et al. and Srinivasan et al. observed a better treatment response with a hypofractionated schedule [9,11]. This might be explained by the fact that a high dose per fraction (e.g. more than 10 Gy) could cause significant more damage in tumour vascularization within 24–48 h after RT compared to a low dose per fraction, as investigated in animal models [33,34]. This might indicate that short course RT with a high dose per fraction is more effective for bleeding tumours.

There are some limitations with regard to our study. First, only 34% of the NVRO members filled out the questionnaire. Although this might question the representativeness of these study results, respondents from 20 out of 21 RT departments filled out the questionnaire and hence this may indicate that these results are representative for the Netherlands. Moreover, the current response is comparable with a previous international questionnaire on nausea and vomiting, also distributed among members of the NVRO [31]. Secondly, the questionnaire was only filled in by radiation oncologists and trainees. This certainly might influence the chosen treatment being radiotherapy. Other treatment modalities as surgery, embolization and other treatments are not investigated in this study. For feasibility purposes the questionnaire was limited to 31 questions and additional questions considering more influencing factors (*e.g.* acute toxicity) that might have been relevant, and more patient case scenarios, were not incorporated in the survey. Furthermore, there was limited response for the questions about expected treatment response. This might be because they were open-ended questions and/or respondents felt not confident answering these questions.

There is limited evidence that a short schedule is as effective as a more fractionated schedule.

Tey *et al.* observed no dose-relationship in a group of 33 patients treated for gastric cancer with palliative intent, of whom 17 had bleeding as key symptom. The median biologically effective dose (BED) in this group was 39 Gy (10 times 3 Gy using a tumour α/β of 10). In the group of patients receiving a BED $\geq$ 39 Gy 7 out of 17 responded and in the group receiving a BED < 39 Gy 6 out of 7 showed a response (p = NS) [24]. In a recent publication of Sapienza *et al*, the authors describe the results of a single center study with a large group of patients [18]. In this cohort of 112 patients, bleeding control information was available for 100 patients. No effect of BED (BED $\geq$ 39 vs BED < 39 Gy) was observed on the primary bleeding control ($p < 0.099$) or on rebleeding rate ($p = 0.36$). Prospective studies to further investigate the effectiveness of currently used schedules are recommended. If single fraction or short course RT (5 fractions) is as effective as longer regimens (ten or more fractions), implementation of short RT schedules is recommended. Here, the comparison to bone metastases is applicable, were a single fraction is the standard RT scheme for relief of pain [27]. Furthermore, single fraction or short regimens are of benefit for both patients, their caregivers (less time consuming) and RT departments (resources).

In conclusion, the current patterns of practice of palliative RT for bleeding tumours in the Netherlands were investigated. The survey showed that a single fraction RT schedule was preferred, followed by a five-fraction RT schedule and that the choice of RT schedule is mainly influenced by patient related factors. However, no conclusion can be drawn from our study with regard to the most optimal RT schedule for bleeding tumours in terms of treatment response, time to treatment response and duration of treatment response. Therefore, it is recommended to further investigate the effectiveness of specific RT schedules, e.g. a prospective cohort study, with the ultimate goal to develop a guideline for bleeding tumours.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2019.01.004.

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