Original Research Article

Short-course palliative radiation therapy leads to excellent bleeding control: A single centre retrospective study

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A B S T R A C T

Purpose: To compare and evaluate the utility of varying hemostatic radiotherapy prescriptions for emergent palliation of bleeding tumors.

Materials and methods: This retrospective study analyzed 112 consecutive patients treated with radiotherapy for emergent palliation of bleeding tumors at an academic institution. Study endpoints included: primary bleeding control; re-bleeding rate after initial control; treatment interruption rate; overall survival; and death within 30 days of treatment.

Results: The most commonly prescribed fractionations were: 20 Gy in 5 fractions, 30 Gy in 10 fractions, and 8 Gy in a single fraction. The overall primary bleeding control rate was 89%. By location, primary bleeding control rates were 89% (31/35), 80% (16/20), 88% (14/16), 93% (13/14), 100% (9/9), and 100% (6/6) for gastrointestinal, genitourinary, head and neck, thoracic, extremity, and gynecologic sites, respectively. The overall re-bleeding rate following initial bleeding control was 25%. Female patients had a significantly reduced risk of bleeding recurrence (HR 0.18 [0.04–0.79], p = 0.02). Longer fractionation regimens (>5 fractions) were not associated with a reduced incidence of re-bleeding (p = 0.65), but were associated with more treatment interruptions (p = 0.02). The 1-year overall survival rate in this population was 24%, with mortality greater in patients with poor performance status (HR 2.99 [1.36–6.58], p = 0.007).

Conclusions: Regardless of prescription, palliative radiotherapy is highly effective for primary bleeding control, with both long and short regimens demonstrating equal hemostatic effect and durability in the emergent setting. Longer radiotherapy regimens (>5 fractions), however, are accompanied by increased treatment interruptions and hospital days. Therefore, shorter hemostatic regimens (<5 fractions) are preferable in this palliative setting, with respect to minimizing treatment burden for patients while achieving symptomatic relief.

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1. Introduction

Bleeding is a common oncologic emergency in patients with locally advanced and/or metastatic cancer treated by radiation oncologists, alongside spinal cord compression, superior vena cava syndrome, and airway obstruction. All require prompt recognition and effective treatment.

The origin of bleeding can be from virtually any body site; however, most of the published literature is related to the female gynecologic tract [1], gastrointestinal tract [2], and lower airways [3,4]. Of these, only the bleeding that originates from the airways (hemoptysis) has been investigated with prospective studies comparing fractionation schemes and providing data on symptom relief [3]. Despite the fact that a significant portion of radiotherapy (RT) is delivered with palliative intent [5], research in this area has been limited over time. Shi et al. [6] showed that less than 5% of the recent manuscripts published in the journals of the American Society for Therapeutic Radiation Oncology (ASTRO) and the European Society
for Radiotherapy and Oncology (ESTRO) focus on symptom control and palliative care. Published studies focusing on the treatment of oncologic urgencies and/or hemostatic radiotherapy are even rarer. Additional evidence is needed in the palliative care field to optimize the management of these patients particularly at the end of life [7]. A well-designed analysis of the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database [8] demonstrated that one in five patients who received radiotherapy in their final 30 days of life spent more than 10 of those days receiving treatment. Concerning the subgroup of patients demanding hemostatic RT who frequently present with locally advanced and/or metastatic disease, the prognosis is predicted to be limited in terms of survival. In this scenario, the use of protracted radiotherapy schedules in the last days of life, as well as the incidence of definitive treatment interruptions, may be used as surrogates to evaluate the appropriateness of a chosen RT prescription.

Thus, the main objectives of the present study were: (1) to evaluate the effectiveness of hemostatic radiotherapy in resolving bleeding; and (2) to analyze potential associations of factors, such as number of fractions, with bleeding control, treatment interruption rates, and death, in order to help radiation oncologists in the decision-making process regarding palliative hemostatic radiotherapy.

2. Materials and methods

This retrospective study included 112 consecutive patients that received hemostatic external beam palliative RT in the urgent setting during the period of April 2012 to May 2015 at a single tertiary oncology center. The patients were directed to the Radiation Oncology Department via the on-call system that serves the emergency department and inpatients. Superficial (cutaneous) bleeding from tumors located in the extremities and head and neck region were included in the respective category. The institutional review board (IRB) approved this study design and the use of patient information without individual identification.

2.1. Endpoints

Primary bleeding control and treatment interruption were dichotomized endpoints. Only patients with clinically detected complete bleeding control were considered to have achieved primary bleeding control (excluding cases that had a definitive treatment interruption). Any grade of partial response or sequential use of other methods (e.g. arterial embolization) were considered a failure to achieve primary bleeding control. In this study, treatment interruption is defined as the definitive suspension of the treatment (not treatment pause). Re-bleeding rate (i.e. the inverse of survival without rebleeding) and overall survival were time-to-event endpoints, calculated from the initial date of arrival to the Radiation Oncology Department (which was the date of the beginning of the treatment for the majority of patients in the urgent setting). The re-bleeding rate was determined in the group of patients who achieved initial bleeding control after treatment. There was no complete information about the hemoglobin level or the use and/or quantity of blood transfusions or other non-invasive measures. In this retrospective study, follow-up schedules varied among patients, depending on treatment site, provider preference, and other clinical factors.

2.2. Subgroup analysis

The subgroup analyses were performed using the following dichotomized variables: gender (male vs. female), age (<70 years old vs. >70 years old), Karnofsky performance status (KPS) (<50 vs. ≥50), histology (squamous cell carcinoma [SCC] vs. non-SCC), tumor site (gastrointestinal and genito-urinary vs. other sites), number metastatic sites (≤1 vs. >1), diagnosis in the urgency (yes vs. no), previous palliative radiotherapy (RT) course to any site (yes vs. no), previous chemotherapy use (yes vs. no), radiotherapy technique (x-ray [2D] vs. CT-scan planning [3D]), biological equivalent dose for alpha/beta ratio of 10 (BED ≤ 39 Gy10 vs. BED > 39 Gy10), and number of fractions (≤5 vs. >5).

2.3. Statistical analysis

The characteristics of the patients treated with abbreviated or protracted schedules were analyzed using the Fisher's exact test for dichotomized variables. The Fisher's exact test was also used to initially analyze univariate associations of the categorical variables with respect to the primary bleeding control, treatment interruption, and death within 30 days of RT endpoints. From the initial screen based on the results of the univariate analysis, variables with \( p < 0.25 \) were incorporated in the multivariate model (binary logistic regression for the dichotomized endpoints or adjusted Cox regression model for the time-dependent endpoints). The time-dependent re-bleeding and overall survival analyses were performed using the Kaplan-Meier method, with patient death included as a censoring event. All statistical analyses were performed using IBM SPSS Statistics, version 20.0 Armonk, NY, USA.

3. Results

3.1. Patients and treatment characteristics

The median and mean age of the patients were both 63 years old (SD = 14.4). The bleeding locations were: gastrointestinal tract (\( n = 39 \)), genitourinary tract (\( n = 23 \)), respiratory tract (\( n = 17 \)), head and neck (H&N) region (\( n = 17 \)), extremities (\( n = 9 \)) and gynecological (\( n = 7 \)). Of all patients, only 19% were treated palliatively for bleeding from locally-advanced tumors, in the absence of metastatic disease. The most commonly used fractionations were: 20 Gy in 5 fractions (\( n = 46 \), BED Gy10 = 28), 30 Gy in 10 fractions (\( n = 25 \), BED Gy10 = 39), and single 8 Gy fraction (\( n = 21 \), BED Gy10 = 14.4) (additional information in the Supplementary Material 1-Table A1). Of note, prescription choice in these cases was left to the discretion of the treating radiation oncologist, in absence of an institutional standard for fractionation in this setting.

The subgroups treated with abbreviated fractionations (≤5) and protracted fractionsions (>5) had similar characteristics, with the exception of the calculated BED, which was higher in the protracted group. The only characteristic with missing data (\( n = 72 \)) was the KPS. Other patients and treatment characteristics are available in Table 1.

3.2. Primary bleeding control

The primary bleeding control after radiotherapy was 89%, based on information available from 100 patients. By site, bleeding control was 88.6% (31/35), 80% (16/20), 87.5% (14/16), 92.8% (13/14), 100% (9/9) and 100% (6/6) for gastrointestinal, urinary tract, H&N, respiratory tract, extremities, and gynecological origin, respectively. The 11 cases that presented with failure to achieve primary bleeding control have the following primary diagnosis site/bleeding site: oral cavity cancer/head and neck, solitary fibrous tumor/gastrointestinal tract, stomach cancer/gastrointestinal tract, rectal cancer/genitourinary tract, anal cancer/gastroin-
testinal tract, stomach cancer/gastrointestinal tract, bone sarcoma/respiratory tract, breast cancer/genitourinary tract, oral cavity cancer/head and neck, prostate cancer/genitourinary tract, and bladder cancer/genitourinary tract (more details in the Supplementary Material 1-Table A2).

None of the following factors were associated with primary bleeding control (univariate analysis): gender (p = 0.526), age >70-years-old (p = 0.742), KPS < 50 (p > 0.999), non-SCC histology (p = 0.712), tumor site other than GI or GU (p = 0.521), metastasis to >1 system (p = 0.751), diagnosis in urgency (p = 0.449), previous palliative RT (p > 0.999), previous chemotherapy use (p = 0.497), radiotherapy technique (p > 0.999), BED > 39 Gy10 (p > 0.999), and number of fractions (>5 vs ≤5) (p = 0.497). The bleeding control rate for each fractionation is provided in the Supplementary Material 1-Table A1. Of note, all 21 patients treated with 8 Gy in a single-fraction achieved initial bleeding control.

3.3. Re-bleeding rate

The re-bleeding rate was considered only for the patients that achieved primary bleeding control (n = 89) and had a documented clinical evaluation after treatment (1 patient excluded due to no information about re-bleeding during follow-up). There were 22 re-bleeding events in the 88 evaluated patients (25%). The median time for the patients who experienced re-bleeding was 84 days. The bleeding remained controlled in 83% of the patients at 3 months, 76% of the patients at 6 months and 56.4% of the patients at 12 months (Fig. 1).

Female patients had a significantly reduced risk of a bleeding recurrence event in the adjusted model (HR 0.182 [0.042–0.789], p = 0.023) (Table 2). Treatment regimens with BED > 39 Gy10 were not associated with reduced incidence of re-bleeding (p = 0.363). Additionally, none of the following factors were associated with re-bleeding rate: age >70-years-old (p = 0.379), KPS < 50 (p = 0.951), non-SCC histology (p = 0.416), tumor site other than GI or GU (p = 0.520), metastasis to more than 1 system (p = 0.882), diagnosis in urgency (p = 0.746), previous palliative RT (p = 0.238), previous chemotherapy use (p = 0.372), radiotherapy technique (p = 0.634), and number of fractions (>5 vs ≤5) (p = 0.652).

3.4. Treatment interruptions

The treatment was interrupted in 12 cases (10.7%). The causes were: intensive care unit (ICU) admission with severe reduction in performance status in 8 cases; and death in the inter-fraction period in 4 cases. Treatment schedules with more than five fractions presented a greater chance of treatment interruption when compared to shorter fractionation schemes (22.2% vs 5.3%, p = 0.020) in univariate and multivariate analyses (Supplementary Material 1-Table A3). The other variables tested in the binary logistic regression (gender, age, and diagnosis in urgency) were not related.

### Table 1

Patient and treatment characteristics.

| Characteristic                  | Overall N (%) | ≤5 fractions N (%) | >5 fractions N (%) | ≤5 fractions vs. >5 fractions (p)* |
|--------------------------------|---------------|--------------------|--------------------|-----------------------------------|
| **Gender**                      |               |                    |                    |                                   |
| Male                           | 71 (63.4)     | 47 (61.8)          | 24 (66.7)          | 0.678                             |
| Female                         | 41 (36.6)     | 29 (38.2)          | 12 (33.3)          |                                   |
| **Age**                         |               |                    |                    |                                   |
| <70 years old                  | 69 (61.6)     | 49 (64.5)          | 20 (55.6)          | 0.409                             |
| ≥70 years old                  | 43 (38.4)     | 27 (35.5)          | 16 (44.4)          |                                   |
| **KPS**                         |               |                    |                    |                                   |
| ≥50                            | 63 (87.5)     | 41 (87.2)          | 22 (88)            | >0.999                            |
| <50                            | 9 (12.5)      | 6 (12.8)           | 3 (12)             |                                   |
| **Histology**                   |               |                    |                    |                                   |
| SCC                            | 24 (21.4)     | 15 (19.7)          | 9 (25)             | 0.623                             |
| No SCC                         | 88 (78.6)     | 61 (81.3)          | 27 (75)            |                                   |
| **Tumor site**                  |               |                    |                    |                                   |
| GI or GU                       | 43 (38.4)     | 30 (39.4)          | 13 (36.1)          | 0.836                             |
| other                          | 69 (61.6)     | 46 (60.6)          | 23 (63.9)          |                                   |
| **Number of metastatic systems**|               |                    |                    |                                   |
| ≤1                             | 59 (52.7)     | 40 (52.6)          | 19 (52.8)          | >0.999                            |
| >1                             | 53 (47.3)     | 36 (47.4)          | 17 (47.2)          |                                   |
| **Diagnosis in urgency**        |               |                    |                    |                                   |
| no                             | 104 (92.8)    | 71 (93.4)          | 33 (91.6)          | 0.710                             |
| yes                            | 8 (7.2)       | 5 (6.6)            | 3 (8.4)            |                                   |
| **Previous palliative RT**     |               |                    |                    |                                   |
| no                             | 99 (88.4)     | 66 (86.8)          | 33 (91.6)          | 0.544                             |
| yes                            | 13 (11.6)     | 10 (13.2)          | 3 (8.4)            |                                   |
| **Previous chemotherapy**       |               |                    |                    |                                   |
| no                             | 38 (33.9)     | 25 (32.9)          | 13 (36.1)          | 0.831                             |
| yes                            | 74 (66.1)     | 51 (67.1)          | 23 (63.9)          |                                   |
| **RT technique**               |               |                    |                    |                                   |
| 2D                             | 93 (83)       | 66 (86.8)          | 27 (75)            | 0.176                             |
| 3D                             | 19 (17)       | 10 (13.2)          | 9 (25)             |                                   |
| **BED**                        |               |                    |                    |                                   |
| ≤39 Gy10                       | 102 (91)      | 75 (98.7)          | 27 (75%)           | <0.001                            |
| >39 Gy10                       | 10 (9)        | 1 (1.3)            | 9 (25%)            |                                   |

KPS: Karnofsky performance status. SCC: squamous cell carcinoma. GI: gastrointestinal. GU: genitourinary. RT: radiotherapy. BED: biological equivalent dose. *2-sided Fisher’s exact test.
**Fig. 1.** Overall re-bleeding rate in the patients that achieved initial bleeding control after hemostatic radiotherapy (n = 88).

**Table 2**
Univariate and multivariate analysis for re-bleeding rate.

| Variable                      | Category     | Univariate analysis | Multivariate analysis |
|-------------------------------|--------------|---------------------|-----------------------|
|                               | n | HR  | CI (95%) | p  | n | HR  | CI (95%) | p  |
| Gender                        |   |     |          |    |   |     |          |    |
| male                          | 35 | 1   | ref      | 0.013 | 35 | 0.182 | 0.042–0.789 | 0.023 |
| female                        | 53 | 0.158 | 0.003–0.683 | 0.158 | 53 | 0.182 | 0.042–0.789 | 0.023 |
| Age                           |   |     |          |    |   |     |          |    |
| <70 y                         | 54 | 1   | ref      | 0.379 | 54 | 0.182 | 0.042–0.789 | 0.023 |
| >70 y                         | 34 | 0.667 | 0.270–1.646 | 0.667 | 34 | 0.182 | 0.042–0.789 | 0.023 |
| KPS                           |   |     |          |    |   |     |          |    |
| ≥50                           | 49 | 1   | ref      | 0.951 | 49 | 0.182 | 0.042–0.789 | 0.023 |
| <50                           | 5  | 1.066 | 0.137–8.264 | 0.951 | 5  | 0.182 | 0.042–0.789 | 0.023 |
| Histology                     |   |     |          |    |   |     |          |    |
| SCC                           | 20 | 1   | ref      | 0.416 | 20 | 0.182 | 0.042–0.789 | 0.023 |
| Non-SCC                       | 68 | 0.674 | 0.261–1.740 | 0.416 | 68 | 0.182 | 0.042–0.789 | 0.023 |
| Tumor site GI or GU           |   |     |          |    |   |     |          |    |
| yes                           | 52 | 1   | ref      | 0.520 | 52 | 0.182 | 0.042–0.789 | 0.023 |
| no                            | 36 | 0.759 | 0.328–1.750 | 0.520 | 36 | 0.182 | 0.042–0.789 | 0.023 |
| Metastasis to more than 1 system |   |     |          |    |   |     |          |    |
| no                            | 48 | 1   | ref      | 0.882 | 48 | 0.182 | 0.042–0.789 | 0.023 |
| yes                           | 40 | 1.067 | 0.453–2.512 | 0.882 | 40 | 0.182 | 0.042–0.789 | 0.023 |
| Diagnosis in urgency          |   |     |          |    |   |     |          |    |
| no                            | 84 | 1   | ref      | 0.746 | 84 | 0.182 | 0.042–0.789 | 0.023 |
| yes                           | 4  | 1.340 | 0.186–10.41 | 0.746 | 4  | 0.182 | 0.042–0.789 | 0.023 |
| Previous palliative RT        |   |     |          |    |   |     |          |    |
| no                            | 77 | 1   | ref      | 0.224 | 77 | 0.182 | 0.042–0.789 | 0.023 |
| yes                           | 11 | 0.286 | 0.038–2.148 | 0.224 | 11 | 0.182 | 0.042–0.789 | 0.023 |
| Previous chemotherapy         |   |     |          |    |   |     |          |    |
| no                            | 28 | 1   | ref      | 0.372 | 28 | 0.182 | 0.042–0.789 | 0.023 |
| yes                           | 60 | 1.542 | 0.596–3.991 | 0.372 | 60 | 0.182 | 0.042–0.789 | 0.023 |
| RT technique                  |   |     |          |    |   |     |          |    |
| 2D                            | 73 | 1   | ref      | 0.634 | 73 | 0.182 | 0.042–0.789 | 0.023 |
| 3D                            | 15 | 1.303 | 0.438–3.873 | 0.634 | 15 | 0.182 | 0.042–0.789 | 0.023 |
| BED                           |   |     |          |    |   |     |          |    |
| ≤39 Gy10                      | 81 | 1   | ref      | 0.634 | 81 | 0.182 | 0.042–0.789 | 0.023 |
| >39 Gy10                      | 7  | 0.304 | 0.041–2.275 | 0.634 | 7  | 0.182 | 0.042–0.789 | 0.023 |
| Number of fractions           |   |     |          |    |   |     |          |    |
| ≤5                            | 60 | 1   | ref      | 0.652 | 60 | 0.182 | 0.042–0.789 | 0.023 |
| >5                            | 28 | 0.818 | 0.342–1.956 | 0.652 | 28 | 0.182 | 0.042–0.789 | 0.023 |

KPS: Karnofsky performance status. SCC: squamous cell carcinoma. GI: gastrointestinal. GU: genitourinary. RT: radiotherapy. BED: biological equivalent dose. HR: Hazard ratio.
3.5. Survival

At the date of our analysis, 73.2% of the patients (82/112) had died and the median follow-up for the entire group was 113 days. The 6-month, 12-month, and 24-month overall survival rates for the whole cohort (n = 112) were 39.5%, 24.3%, and 12.6%, respectively (Kaplan Meier analysis in the Supplementary Material 2). Both lower performance status (KPS < 50) and metastasis to more than 1 distant site were significantly associated with worse OS in the univariate analysis (Table 3). However, only KPS remained significant (HR 2.994 [1.355–6.578], p = 0.007) in the multivariate model.

Twenty-five patients (22.3%) died within 1 month of the beginning of the treatment. Initial diagnosis at presentation (p = 0.024) was the only factor associated with death within 30-days of RT (Table 4). Additionally, number of fractions was not significantly associated with death within 30-days of RT on univariate (p = 0.155) or multivariate (p = 0.220) analysis.

4. Discussion

The present study shows that the use of hemostatic radiotherapy is effective and provides excellent primary bleeding control, with an overall rate of 89%, varying from 80% to 100% depending on the site of bleeding. The rates by site are comparable with the notion— that a higher BED or longer fractionation regimen is not associated with hemostatic effect— is analogous to the findings of palliative radiotherapy for pain in bone metastases [15]. Our analysis did not find a significant difference between regimens with lower BED versus those with higher BED in terms of re-bleeding rate. In the case of bone metastases, single fraction schemes resulted in re-treatment rates in the order of 20–24% for single fraction compared to 6–8% for multiple fraction regimens; however, re-treatment rates of previous studies were found to be skewed by provider disbelief in the adequacy of single-fraction prescriptions and increased willingness to retreat following single-fraction [16,17]. Furthermore, an analysis of international practice patterns of palliative radiotherapy found that most radiation oncologists continue to prescribe multi-fraction regimens for patients who meet eligibility criteria for single-fraction treatment [18].

In the current study KPS < 50 was the only parameter associated with inferior overall survival (HR 2.994 [1.355–6.578], p = 0.007). Consistent with these findings, Cihoric et al. [19] found 85% Table 3

| Variable | Category | Univariate analysis | Multivariate analysis |
|----------|----------|---------------------|----------------------|
|          |          | n | HR | CI (95%) | p | n | HR | CI (95%) | p |
| Gender   | male     | 41 | 1 | ref |     | 35 | 1 | ref |     |
|          | female   | 71 | 0.913 | 0.581–1.435 | 0.639 | 37 | 1.697 | 0.925–3.115 | 0.087 |
| Age      | <70 y    | 69 | 1 | ref |     | 48 | 1 |     |     |
|          | >70 y    | 43 | 0.734 | 0.463–1.162 | 0.187 | 24 | 0.636 | 0.330–1.228 | 0.178 |
| KPS      | ≥50      | 63 | 1 | ref |     | 63 | 1 | ref |     |
|          | <50      | 9 | 2.710 | 1.257–5.847 | 0.011 | 9 | 2.994 | 1.355–6.578 | 0.007 |
| Histology| SCC      | 24 | 1 | ref |     | 25 | 1 | ref |     |
|          | Non-SCC  | 88 | 1.002 | 0.577–1.739 | 0.995 | – | – | – | – |
| Tumor site| GI or GI | 69 | 1 | ref |     | 56 | 1 | ref |     |
|          | Non-GI or GU | 43 | 1.088 | 0.695–1.700 | 0.713 | – | – | – | – |
| Metastasis to more than 1 system | no | 59 | 1 | ref |     | 55 | 1 | ref |     |
|          | yes      | 53 | 1.675 | 1.070–2.624 | 0.024 | 37 | 1.697 | 0.925–3.115 | 0.087 |
| Diagnosis in urgency | no | 104 | 1 | ref |     | 65 | 1 | ref |     |
|          | yes      | 8 | 1.721 | 0.791–3.746 | 0.171 | 7 | 1.819 | 0.755–4.383 | 0.182 |
| Previous palliative RT | no | 99 | 1 | ref |     | 69 | 1 | ref |     |
|          | yes      | 13 | 1.136 | 0.97–2.162 | – | 9 | 1 | ref |     |
| Previous chemotherapy | no | 38 | 1 | ref |     | 25 | 1 | ref |     |
|          | yes      | 74 | 1.012 | 0.641–1.595 | – | 25 | 0.834 | 0.441–1.572 | 0.575 |
| RT technique | 2D | 93 | 1 | ref |     | 60 | 1 | ref |     |
|          | 3D       | 19 | 0.679 | 0.374–1.231 | 0.203 | 12 | 0.983 | 0.406–2.380 | 0.970 |
| BED      | ≤39 Gy10 | 102 | 1 | ref |     | 80 | 1 | ref |     |
|          | >39 Gy10 | 10 | 0.745 | 0.334–1.621 | 0.458 | 10 | 1 | ref |     |
| Number of fractions | ≤5 | 76 | 1 | ref | 0.172 | 47 | 1 | ref |     |
|          | >5       | 36 | 0.719 | 0.440–1.153 | – | 1 | ref |     |
KPS: Karnofsky performance status. SCC: squamous cell carcinoma. GI: gastrointestinal. GU: genitourinary. RT: radiotherapy. BED: biological equivalent dose. HR: Hazard ratio.
increased risk of death with KPS < 50 (HR 1.855 [0.971–3.533], \( p = 0.061 \)), which might not have reached statistical significance due to the lower number of cases in their study (\( n = 62 \)). However, they found that dose of hemostatic RT < 30 Gy (HR 2.853 [1.360–5.987], \( p = 0.061 \)) and bleeding score grade 2–4 at end of treatment (HR 6.456 [2.645–16.202], \( p = 0.061 \)) negatively influenced survival. Of note, the significance of performance status was recently highlighted in a large prospective Brazilian study (PROGRAD) [20], which evaluated the prognosis of inpatients assessed for palliative RT using two prediction scores [21,22].

Although the proportion of patients receiving protracted regimens is intuitively expected to be lower for the subgroup with limited survival, our data indicates a lack of significant association between the two factors (\( p = 0.155 \)). This fact, combined with the increased frequency of treatment interruptions in patients treated with >5 fractions (22.2% vs. 5.3%, \( p = 0.020 \)), underline the notion that protracted fractionation schedules are less favorable in the palliative hemostatic setting.

The main limitation of the present study was its retrospective nature. Treatment indication and prescription were based on clinical judgment and thus possibly influenced by patient performance status and extent of the bleeding focus (tumor volume); however, in our study all the characteristics of the patients treated with shorter fractionations were similar to the ones treated with protracted regimens. Another limitation is the lack of other bleeding control assessments, such as hematologic level or transfusions required, which would provide an extra layer of information on this topic if available. Finally, another limitation of this report is the lack of treatment-related side-effect profiles, although toxicity rates would be presumably decreased in the lower dose regimens and perhaps better-tolerated than protracted regimens, particularly when considering the equivalent palliative benefit [9].

In conclusion, independent of the fractionation regimen, radiation therapy was effective in resolving bleeding from malignant tumors in the urgent scenario, with nearly 90% of cases achieving resolution. However, the risk of treatment discontinuation was greater with protracted schedules (>5 fractions). In practical terms, the use of shorter fractionation schedules (e.g.: single 8 Gy fraction or 20 Gy in 5 fractions) minimizes the portion of final days of life spent outside a hospital and is most consistent with palliative principles. Our findings thus provide guidance to physicians faced with the difficult choice of treatment intensity in this palliative hemostatic setting. As nearly 50% and 14% of the patients receive RT within the last 6 months and 14 days of life, respectively [23], further studies with validated end-points could provide guidance for optimal fractionation choices in different palliative scenarios, with respect to minimizing treatment burden for patients while achieving symptomatic relief.

Conflicts of interest(s)
None.

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Appendix A. Supplementary material
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2018.11.007.

References
[1] van Lonkhuijzen L, Thomas G. Palliative radiotherapy for cervical carcinoma, a systematic review. Radiother Oncol 2011;98:287–91.
[2] Tey J, Soon YY, Koh WY, et al. Palliative radiotherapy for gastric cancer: a systematic review and meta-analysis. Oncotarget 2017;8(15):25797–805.
[3] Rodrigues G, Velez A, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: an American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol 2011;1(2):60–71.
[4] Ung YC, Yu E, Falkson C, et al. The role of high-dose-rate brachytherapy in the palliation of symptoms in patients with non-small-cell lung cancer: a systematic review. Brachytherapy 2006;5:189–202.
[5] Tseng YD, Krishnan MS, Jones JA, et al. Supportive and palliative radiation oncology service: impact of a dedicated service on palliative cancer care. Pract Radiat Oncol 2014;4:247–51.
[6] Shi DD, DiGiovanni J, Skamene S, et al. Patterns of symptom control and palliative care-focused original research articles in the International Journal of Radiation Oncology * Biology* Physics and the Radiation Oncology Oncology Journal, 2005–2014. Ann Palliat Med 2018;7(2):249–55.
[7] Jones JA, Lutz ST, Chow E, Johnston PA. Palliative radiotherapy at the end of life: a critical review. CA Cancer J Clin 2014;64(5):296–310.
[8] Guadagno BA, Liao KP, Efird TL, et al. Use of radiation therapy in the last 30 days of life among a large population-based cohort of elderly patients in the United States. J Clin Oncol 2012;31(1):80–7.
[9] Picardi V, Deodato F, Guido A, et al. Palliative short-course radiation therapy in rectal cancer: a phase 2 study. Int J Radiat Oncol Biol Phys 2016;95(4):1184–90.
[10] Tey J, Choo BA, Leong CN, et al. Clinical outcome of palliative radiotherapy for locally advanced symptomatic gastric cancer in the modern era. Medicine 2014;93(22):e118.

Table 4
Factor associated with precocious death (in the first 30 days after the beginning of the treatment).

| Variable                        | Categories          | Treatment Interruptions | Univariate analysis* | Multivariate analysis** |
|--------------------------------|---------------------|-------------------------|----------------------|-------------------------|
| Gender                         | Female vs. male     | 112                     | 0.814                |                         |
| Age                            | >70y vs. <70y       | 112                     | >0.999               |                         |
| KPS                            | < 50 vs. > 50       | 72                      | 0.083                | 72                      | 0.104                  |
| Histology                      | Non-SCC vs. SCC     | 112                     | 0.585                |                         |
| Tumor site GI or GU            | No vs. yes          | 112                     | 0.494                |                         |
| Metastasis to > 1 system       | Yes vs. no          | 112                     | 0.497                |                         |
| Diagnosis in urgency           | Yes vs. no          | 112                     | 0.013                | 72                      | 0.024                  |
| Previous palliative RT         | Yes vs. no          | 112                     | 0.729                |                         |
| Previous chemotherapy          | Yes vs. no          | 112                     | 0.481                |                         |
| RT technique                   | 3D vs. 2D           | 112                     | 0.068                | 72                      | 0.405                  |
| BED                            | >39 Gy<sub>10</sub> vs. \(< 39 \text{ Gy}<s2/>\text{10} \>39 \text{ Gy}<s2/>\text{10}\) | 72                     | >0.999               |                         |
| Number of fractions            | >5 vs. \(< 5 \)    | 112                     | 0.155                | 72                      | 0.220                  |

KPS: Karnofsky performance status. SCC: squamous cell carcinoma. GI: gastrointestinal. GU: genitourinary. RT: radiotherapy. BED: biological equivalent dose. * Fisher exact test. ** Binary logistic regression.
[11] Lee YH, Lee JW, Jang HS. Palliative external beam radiotherapy for the treatment of tumor bleeding in inoperable advanced gastric cancer. BMC Cancer 2017;17:541.

[12] Dirix P, Vingerhoedt S, Joniau S, Van Cleynenbreugel B, Haustermans K. Hypofractionated palliative radiotherapy for bladder cancer. Support Cancer Care 2016;24(1):181–6.

[13] Kramer GWPM, Gans S, Ullmann E, et al. Hypofractionated external beam radiotherapy as retreatment for symptomatic non-small-cell lung carcinoma: an effective treatment? Int J Radiat Oncol Biol Phys 2004;58(5):1388–93.

[14] Kim DH, Lee JH, Ki YK, et al. Short-course palliative radiotherapy for uterine cervical cancer. Radiat Oncol J 2013;31(4):216–21.

[15] Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. Pract Radiat Oncol 2017;7(1):4–12.

[16] Rich SE, Chow R, Raman S, et al. Update of the systematic review of palliative radiation therapy fractionation for bone metastases. Radiother Oncol 2018;126(3):547–57.

[17] van der Linden YM, Lok JJ, Steenland E, et al. Single fraction radiotherapy is efficacious: a further analysis of the Dutch Bone Metastasis Study controlling for the influence of retreatment. Int J Radiat Oncol Biol Phys. 2004;59(2):528–37.

[18] Fairchild A, Barnes E, Ghosh S, et al. International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice? Int J Radiat Oncol Biol Phys. 2009;75(5):1501–10.

[19] Cihoric N, Crowe S, Eychmüller S, Aebersold DM, Ghadjar P. Clinically significant bleeding in incurable cancer patients: effectiveness of hemostatic radiotherapy. Radiat Oncol 2012;7:132.

[20] Chen ATC, Mauro GP, Gabrieli F, et al. PROGRAD - An observational study of the prognosis of inpatients evaluated for palliative radiotherapy. Radiother Oncol 2018;127(2):299–303.

[21] Morita T, Tsunoda J, Inoue S, Chihara S. The Palliative Prognostic Index: a scoring system for survival prediction of terminally ill cancer patients. Support Care Cancer 1999;7(3):128–33.

[22] Chow E, Abdolell M, Panzarella T, et al. Predictive model for survival in patients with advanced cancer. J Clin Oncol 2008;26(36):5863–9.

[23] Kress MAS, Jensen RE, Tsai HT, et al. Radiation therapy at the end of life: a population-based study examining palliative treatment intensity. Radiat Oncol 2015;10:15.