



Emergent radiotherapy for pelvic malignancies: a narrative review

Kristopher Dennis^{1^}, Risa Shorr², Said Al Saifi¹, Rajiv Samant¹, Scott Morgan¹

¹Division of Radiation Oncology, The Ottawa Hospital and the University of Ottawa, Ottawa, Canada; ²The Ottawa Hospital, Ottawa, Canada

Contributions: (I) Conception and design: K Dennis, R Shorr, R Samant, S Morgan; (II) Administrative support: K Dennis, R Shorr, S Al Saifi; (III) Provision of study materials or patients: K Dennis, R Shorr, S Al Saifi; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kristopher Dennis, MD, FRCPC, PhD. Division of Radiation Oncology, The Ottawa Hospital and the University of Ottawa, 501 Smyth Rd, Ottawa K1H8L6, Canada. Email: krdennis@toh.ca.

Background and Objective: Patients with primary genitourinary (GU), gynecologic (GYN) and gastrointestinal (GI) cancers can develop life-threatening or critical function-threatening symptoms that necessitate emergent intervention with palliative radiotherapy (RT). Unfortunately, research describing the use of RT in this critical setting is lacking. We aimed to review literature describing emergent palliative RT for primary pelvic malignancies and provide a narrative synthesis of relevant studies.

Methods: A medical librarian searched Ovid MEDLINE, Embase Classic, and Embase databases for relevant English language references from 1946–2022. No restrictions were placed on study type, publication type or date. References for GU, GYN and GI cancers were grouped and synthesized separately.

Key Content and Findings: The treatment of bleeding from primary pelvic tumors was the only indication for emergent RT identified, however, no references reported dedicated cohorts of patients treated for bleeding in the emergent setting. Most references were retrospective single institution studies describing various dose fractionation schemes for non-emergent palliative RT. Outcome measures and response assessment times varied. The latency to hemostasis after RT commencement was not well described; most studies reported outcomes captured weeks or months following treatment. In general, high rates of hemostasis for GU, GYN and GI tumors have been reported following RT schedules ranging from a single fraction to many weeks of fractionated treatments. Bleeding seems to respond more favorably than other symptoms including pain and obstruction.

Conclusions: Managing bleeding was the only indication for emergent RT identified in our search. Scant data exist that describe the latency to a hemostatic response following RT. This is an important knowledge gap in the literature given how commonly patients are affected by this complication of primary pelvic malignancies.

Keywords: Hemorrhage; oncologic emergency; palliative care; pelvic neoplasms; radiotherapy (RT)

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Introduction

Background

Patients with primary pelvic genitourinary (GU), gynecologic (GYN) and gastrointestinal (GI) cancers, whether early- or advanced-stage can develop sudden-

onset symptoms and present in need of expedited care. Tumors can cause pain due to inflammation, mass effect, and invasion of surrounding structures, they can obstruct or compromise normal flow through GU and GI luminal structures, and they can bleed, putting patients at risk of the potentially dangerous complications of excessive blood loss.

[^] ORCID: 0000-0002-5588-1007.

Rationale and knowledge gap

Radiotherapy (RT) is a mainstay treatment in the palliative management of patients with symptoms from primary pelvic malignancies. A limited number of randomized trials, reviews and practice guidelines exist to aid practitioners in delivering standard non-emergent palliative RT regimens to some of these tumors, however, to our knowledge, reports investigating ideal parameters for RT in the emergent setting are lacking. The acute management of patients with life-threatening or critical function-threatening symptoms caused by primary pelvic malignancies often involves delivering emergent RT, making the apparent lack of related literature in this space an important knowledge gap.

Objective

We provide commentary while highlighting literature relevant to the practice of emergent RT for primary pelvic malignancies. Treatments for pelvic bone metastases and pelvic hematologic malignancies are described in other chapters. Where possible, we discuss prospective studies, systematic reviews and clinical practice guidelines. Where such data is lacking, we discuss retrospective series. We aimed to address this knowledge gap, and we present this article in accordance with the Narrative Review reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-23-67/rc>).

Methods

Literature search

A medical librarian (Risa Shorr) searched Ovid MEDLINE, Embase Classic, and Embase databases for references relevant to emergent RT for primary pelvic malignancies. After piloting several strategies and gaining an understanding that the management of bleeding would be our main focus, two unique searches were conducted that formed the basis for this review. The first searched references from 1946 to 16 June 2022 and focused on the management (with RT) of emergencies not otherwise specified resulting from primary pelvic malignancies and the second searched references from 1946 to 20 June 2022 and focused on the management (with RT) of bleeding and/or hemorrhage related to those tumors. Only English language references were retained, but no restrictions were placed on the type of study, or publication type or date. References returned by the searches were screened

independently by two authors (K.D., S.A.S.) and all references deemed potentially relevant to the emergent use of RT for primary pelvic malignancies, regardless of the study design or year of publication by either author had their full articles retrieved for review. Summaries of the searches are shown in *Table 1* and their full search strategies are shown in *Appendix 1*.

Findings

The search focusing on emergencies not otherwise specified returned 189 references and the search focusing on bleeding/hemorrhage returned 410 references. Fifty-one references underwent full-article review. As expected, we found that no articles dealt directly with the role of emergent RT in the management of bleeding or other symptoms from primary pelvic tumors. Most references described cohorts of patients that received non-emergent palliative RT regimens, patterns of emergency department use among patients with primary pelvic malignancies, treatment strategies for the management of pelvic recurrences, and complications resulting from pelvic RT and other anti-cancer treatments that result in patients seeking urgent or emergent care but not RT.

Emergent palliative pelvic RT is seldom used for reasons other than compression of the cauda equina or bleeding. The incidence of former event is described in another chapter, but concerning the latter, Mitera and colleagues reported outcomes of the 161 patients treated emergently on weekends and holidays over a two-year period at a single Canadian tertiary cancer center (1). Only three patients received treatment due to pelvic and/or GI bleeding and a single patient was treated due to malignant bowel obstruction. This review did not capture emergent events treated during normal working hours, but presumably the distribution of indications would be similar.

Whereas bleeding from pelvic malignancies is an indication for emergent RT, pain and obstruction are not. Patients with most solid tumors need to wait weeks following RT to notice improvements in pain (whether from primary malignancies or bone metastases) or obstructions of GU and GI structures. Conversely, complete or partial hemostasis can be achieved within days of initiating RT. Tumors with mucosal (i.e., oozing) bleeding respond more reliably to RT than those with pulsatile bleeding from hemorrhaging vessels. The latter type requires more invasive treatment with surgery, endoscopy and/or interventional radiology; articles describing RT to manage

Table 1 Summary of literature searches

Items	Specification
Date of search	16-June-2022, 20-June-2022
Databases and other sources searched	Ovid MEDLINE, Embase Classic, Embase
Search terms used	See Appendix 1
Timeframe	1946 to June 2022
Inclusion and exclusion criteria	<p>Included</p> <ul style="list-style-type: none"> • 1st search: references pertaining to the radiotherapeutic management of emergencies resulting from primary pelvic malignancies • 2nd search: references pertaining to the radiotherapeutic management of bleeding/hemorrhage resulting from primary pelvic malignancies <p>Excluded: non-English references, references pertaining to emergencies resulting from bone metastases and pelvic hematologic primary malignancies</p>
Selection process	Screening captured any references relevant to inclusion criteria, regardless of article type, for full article review. Author performing database search: Risa Shorr; Authors performing screening: K.D., S.A.S.

this type of bleeding were not found.

The following sub-sections describe select references from our literature searches that report data most relevant to the emergent radiotherapeutic management of bleeding from primary pelvic GU, GYN and GI malignancies (*Table 2*). References describing symptom outcomes captured soon after RT completion are prioritized over those describing outcomes captured months afterwards.

GU cancers

Tey and colleagues published a systematic review and meta-analysis of articles from 1990–2019 that described palliative RT for bladder cancer (2). Their analysis focused primarily on response rates for hematuria, dysuria and frequency. They identified one randomized, four prospective and eight retrospective non-comparative studies that cumulatively described outcomes for 1,320 patients. Total doses ranged from 8–60 Gy in fraction sizes of 2–8 Gy. No concurrent chemotherapy was administered. The pooled response rate for bleeding was 74%. Schedules with higher biologically-equivalent doses (BEDs) were not associated with improved bleeding response rates among the 966 patients evaluated, but in two studies (n=58 and 67) a higher BED was associated with a more durable response (4,5). The authors were not able to make conclusions about the latency to a hemostatic response following RT initiation.

The BA09 trial from the Medical Research Council

(MRC) Bladder Cancer Working Party randomized 500 patients with symptomatic muscle-invasive bladder cancer to 35 Gy in 10 fractions over 2 weeks or 21 Gy in 3 fractions on alternating days over 1 week (3). Among the 272 patients with available data for the 3-month primary endpoint of overall symptomatic improvement, 68% responded favorably with no differences between study arms for efficacy or toxicity. Of relevance to emergent RT, hematuria specifically had improved by the end of treatment for 55% and 50% of patients in the 35 and 21 Gy arms respectively.

Tey and colleagues published a retrospective report on the hematuria response rates of 58 patients with bladder cancer treated at their institution with palliative RT from 2001–2016 (4). The median survival of all patients was 5.6 months (range, 0–47.6 months). Dose fractionations ranged from 8 Gy in 1 fraction to 40 Gy in 16 fractions. Sixty-two percent of patients received ‘low BED’ therapy (<36 Gy). Overall, 67% of patients responded: 22/36 (61%) with low BED RT and 17/22 (77%) with high BED. The overall median duration of response was 3.7 months (range, 0–44.5 months). Hematuria recurred in 11/22 (50%) of patients in the low BED group and in 2/17 (12%) in the high BED group.

A single institution retrospective study of 67 patients treated with palliative RT between 2002 and 2013 for uncontrolled bleeding from bladder cancer was reported by Aljabab and colleagues (5). A complete hemostatic response was achieved in 73% of patients, a partial

Table 2 Select references relevant to emergent RT for primary pelvic malignancies

Reference	Description
GU malignancies	
Tey 2021 (2)	Systematic review of palliative RT for bladder cancer
Duchesne 2000 (3)	Randomized trial of palliative RT for bladder cancer
Tey 2019 (4)	Retrospective study of palliative RT for bladder cancer
Aljabab 2017 (5)	Retrospective study of hemostatic RT for bladder cancer
Cameron 2014 (6)	Systematic review of palliative RT for prostate cancer
Kamran 2017 (7)	Retrospective study of palliative RT for GU cancers
GYN malignancies	
van Lonkhuijzen 2011 (8)	Systematic review of palliative RT for cervical cancer
Eleje 2015 (9)	Systematic review of hemostatic RT for cervical cancer
Butala 2021 (10)	Retrospective study of hemostatic RT for GYN cancers
Kim 2013 (11)	Retrospective study of palliative RT for cervical cancer
Yan 2011 (12)	Retrospective study of palliative RT for GYN cancers
Kellogg 2020 (13)	Retrospective study of palliative RT for GYN cancers
Jiang 2015 (14)	Retrospective study of palliative RT for ovarian cancer
GI malignancies	
Cameron 2014 (15)	Systematic review of palliative RT for rectal cancer
Cameron 2016 (16)	Prospective study of palliative RT for rectal cancer
Picardi 2016 (17)	Prospective study of palliative RT for rectal cancer
Chia 2016 (18)	Retrospective study of palliative RT for rectal cancer

RT, radiotherapy; GU, genitourinary; GYN, gynecologic; GI, gastrointestinal.

response in 16% and no response in 10%. Among complete responders, the median time at which a response assessment was documented was 37 days following treatment, and the median freedom from recurrent bleeding time was 4.4 months. As with the prior reference, the authors could not report the latency from RT to first hemostatic response so the generalizability of their data to the emergent setting is limited.

Cameron and colleagues published a systematic review of articles up to 2011 that described symptom, quality of life and toxicity outcomes following palliative RT for incurable prostate cancer (6). They identified nine retrospective studies spanning the years 1961–2007 that cumulatively described outcomes for 315 patients. Total doses ranged from 8–76 Gy in fraction sizes of <2–8 Gy. Outcome measures ranged from single symptoms such as ureteric obstruction to multi-factor symptom constellations. Overall symptom response rates ranged from 60–100% with a pooled rate of 75%. The pooled response rate for hematuria specifically was 73% among 80 patients with available data. Hematuria tended to be an early-responding symptom compared to others. No dose response was observed.

RT is also useful for hemostasis in the setting of pelvic re-irradiation for GU cancers. Kamran and colleagues retrospectively reviewed the outcomes of 27 patients treated with palliative RT for local recurrences or second malignancies (7). The median time from initial treatment to re-irradiation was 9.5 years. Although patients were treated aggressively with a median re-irradiation dose of 50 Gy, over half had hematuria at baseline, and essentially all responded to treatment. The times from RT commencement to hemostasis, however, were not available.

GYN cancers

A 2011 systematic review examined studies describing the use of RT for the palliation of symptoms from cervical cancer (8). Only eight references met inclusion criteria, seven of which were retrospective. Study methodologies varied and contained considerable sources of bias. Of the studies that reported outcomes for bleeding specifically, response rates ranged from 45–100% following RT schedules that varied from a single fraction to a schedule where twice-daily fractions were delivered on two

consecutive days and that was repeated at weekly or monthly intervals as necessary. The latency from treatment to hemostasis in these studies could not be reported.

A 2015 Cochrane review of palliative interventions for controlling vaginal bleeding in advanced cervical cancer highlighted the paucity of high-quality data in this area of study (9). The authors did not identify any randomized studies that compared palliative RT with tranexamic acid, vaginal packing, interventional radiology or other interventions. It is unlikely that trials like this will be conducted, however, as these therapies are often combined in the urgent setting.

Butala and colleagues aimed to describe the latency to hemostasis among women with primary or recurrent GYN cancers that received palliative pelvic RT (10). Their single-institution retrospective study identified 33 evaluable women treated between 2010 and 2019 with prescribed doses ranging from 8–50.4 Gy. The median time to any response for the entire cohort was 5 days from the time of RT initiation and 79% of patients had signs of an initial response prior to RT completion. The subset of patients that received short course RT (defined as less than or equal to five fractions, >3.5 Gy/fraction, and ≤ 37.5 BED) responded earlier than those treated with courses longer than 5 fractions, with a median time of 2.5 days from RT initiation compared to 6.

A similar single institution retrospective study described outcomes for 17 patients with cervical cancer treated palliatively with 20–25 Gy in 5 fractions (11). Of the 16 patients with bleeding at baseline, 15 (94%) responded, with a median ‘bleeding control time’ of 3 days after RT initiation (range, 2–7 days).

A retrospective single institution report described outcomes for 51 patients with a variety of pelvic GYN cancers who were prescribed three fractions of palliative RT along a 0–7–21 day schedule with doses of 6–8 Gy per fraction (12). Bleeding was the most common indication for treatment, and at least partial hemostasis was achieved in 92% of patients with available data describing symptom responses. The authors reported how palliation was achieved for many patients following the first fraction (i.e., earlier than 7 days from RT commencement), but the exact latency from that fraction to hemostasis could not be described.

A more recent single institution report described outcomes for 59 patients treated with the Quad Shot schedule wherein cycles of twice-daily RT fractions of 3.7 Gy delivered on 2 consecutive days (four fractions in

total) were repeated several weeks apart as necessary to achieve adequate palliation (13). Bleeding was the most common presenting symptom. Among patients with available follow up data, 84% and 11% had complete and partial relief of symptoms respectively. The time from RT to hemostasis was not reported.

The outcomes for 63 patients with recurrent ovarian cancer that underwent palliative RT at a single institution were retrospectively reviewed by Jiang and colleagues (14). The response rate for bleeding was 93%, and symptom outcomes were generally better for patients with serous and endometrioid histology than for those with clear cell tumors.

GI cancers

A systematic review detailed findings from 27 studies up to 2011 that reported symptomatic or quality of life outcomes following palliative RT for primary or recurrent rectal and rectosigmoid cancers (15). Four prospective and 23 retrospective studies that cumulatively reported on 1,759 patients were analyzed. Only two studies were published after 1990. Total doses ranged from 5–70 Gy. Response criteria varied, and no patient-reported outcomes were used. The pooled response rate for bleeding relief was 81% among the six studies that reported this symptom specifically, however, the timing of onset of that relief could not be determined.

A multi-center prospective study from Norway, published after that review, described outcomes for 51 patients with symptomatic primary or recurrent rectal cancer treated with 30–39 Gy in 3 Gy fractions (16). Of the 9 patients with hematochezia as their target symptom for analysis, all had responded by the planned assessment time at the end of RT. The authors discussed in retrospect how for future patients with bleeding as a target symptom, single large fractions of 8–10 Gy may be most appropriate compared to longer schedules of 10–13 fractions.

A smaller prospective Italian phase II study of 18 patients receiving 25 Gy in 5 fractions of palliative RT for rectal cancer assessed symptom outcomes four weeks following treatment (17). Among the nine patients followed for bleeding, 78% achieved a complete response and 22% a partial response. The times to patients’ first responses were not captured.

A single-institution retrospective study from Singapore described the outcomes of 99 patients with symptomatic rectal cancer that received palliative RT alone (18).

Schedules ranged from 18 Gy in 6 fractions to 54 Gy in 30 fractions. Of the 83 patients with bleeding as an index symptom, 87% responded, with response defined as resolved hematochezia and maintained hemoglobin and no further transfusions. The authors had audited notes taken during RT to assess responses, but the times to initial and/or maximal hemostasis were not described.

Discussion

We believe most radiation oncologists would consider providing timely hemostasis as one of the most expedient, reliable and gratifying benefits of delivering palliative RT. As expected however, our review confirmed a glaring paucity of prospective data describing the latency to hemostasis following RT initiation for bleeding primary pelvic tumors. As with other indications for palliative RT, we do not have a credible body of evidence that supports our collective experiences and anecdotes in this urgent/emergent setting.

The references we highlighted were published over several decades by investigators from multiple continents, which demonstrates how bleeding primary pelvic malignancies remain a challenge to patients and practitioners globally. We found considerable methodological heterogeneity and sources of bias among the studies reviewed. Most were retrospective single-institution reports with variably defined symptom outcome measures captured at different times following RT commencement. The cumulative available data also had limited relevance to the practice of emergent hemostatic RT, as only a few studies reported symptom outcomes from during- or by the end of RT (3,10,11,16). Use of cointerventions such as blood transfusions, endoscopic therapies and vaginal packing that may confound assessment of response to RT were rarely reported, and only a small minority of studies contained patient-reported outcomes.

Patients require thorough investigations and medical management before RT should be considered for hemostasis. Alternative explanations for blood loss and potential contributors to it such as anti-coagulants need to be explored. When the anatomic source of bleeding is unclear, endoscopy can be both diagnostic and therapeutic. The precise locations of tumors can be documented to aid RT treatment planning, and temporizing hemostasis can be achieved via a variety of methods including topical treatments such as hemostatic sprays, injections that achieve mechanical and/or cytochemical hemostasis, thermal

treatments such as multipolar/bipolar probes, argon plasma coagulation, radiofrequency ablation and cryotherapy, and mechanical devices such as clips, sutures, bands and stents.

Despite the knowledge gap concerning the latency to hemostasis, there is evidence in support of a variety of palliative RT schedules for this indication in general and a dose-response relationship for hemostasis is not consistently seen across the literature. This allows for flexibility in patient management, even in the emergent setting. A patient's 'ideal' dose fractionation can be determined by considering a number of factors including their functional status and expected prognosis, the logistics of their care delivery (e.g., inpatient *vs.* outpatient, travel requirements), whether palliative goals aside from hemostasis exist (e.g., pain control, local control), and if complimentary treatments will be administered (e.g., vaginal packing).

For many patients with bleeding primary pelvic tumors that cannot be managed adequately by other means, an emergent single fraction of 8 Gy can be an appropriate first, if not definitive intervention to achieve hemostasis. This dose has a safe and tolerable toxicity profile and is unlikely to meaningfully compromise potential plans for sequential consolidative RT once the patient is stabilized. The schedule is efficient, economical and can be planned and delivered within a few hours. There is also the suggestion that larger fraction sizes might provide more timely hemostasis than smaller sizes (10,19).

We view the inclusive design of our database searches as a strength of this work; it allowed us to capture potentially relevant references ranging from case reports to systematic reviews. The expert skills of a medical librarian also ensured high quality search methods were used. Our results are limited by the paucity of reports describing the use of RT in the emergent setting for primary pelvic tumors; most of the material we discussed was identified within more general palliative RT references, and deemed of indirect relevance to our main research question.

Simple prospective studies could make meaningful contributions to this area of study. Well-defined cohorts of patients could be followed during and following RT to assess their hemostatic responses. Ideally frequent assessments during fractionated courses of treatment would be carried out, but even a single assessment at the end of RT courses would incrementally increase and improve our understanding of how well and when these tumors respond. Standardized measures of response could be used during and following RT that control for potential confounders such as anticoagulants and transfusions. Patient-reported

outcomes could be captured which are lacking in the literature, especially for GI tumors. Descriptions of consolidative therapies including additional fractions of RT could be described for patients without sufficient hemostatic responses, and those requiring more dose for adequate palliation of other symptoms.

Conclusions

Managing bleeding was the only indication for emergent RT identified in our search. A large body of data supports RT in the management of bleeding from primary pelvic malignancies, however, the latency to a hemostatic response is not well-studied. This is an important knowledge gap in the literature given the need to provide timely hemostasis to symptomatic patients. No convincing dose-response relationship for hemostasis was identified.

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Footnote

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Peer Review File: Available at <https://apm.amegroups.com/article/view/10.21037/apm-23-67/prf>

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1 Literature search strategies

I. Literature search strategy for radiotherapeutic management of emergencies resulting from primary pelvic malignancies.

Embase Classic+Embase <1947 to 2022 June 16>

Ovid MEDLINE(R) ALL <1946 to June 16, 2022>

1. exp abdominal neoplasms/ or exp digestive system neoplasms/ or pelvic neoplasms/ or exp urogenital neoplasms/ 3303363
2. ((pelvi* or abdom* or gynecol* or ovarian or gastro* or genitourin* or Urogenital or endometr* or cervical or vagina* or prostat*) adj3 (cancer* or neoplasm* or malignanc*)).tw,kf. 827627
3. 1 or 2. 3451706
4. exp radiotherapy/ 877693
5. (radiation therap* or radiotherap*).tw,kf. 695967
6. 4 or 5. 1148333
7. 3 and 6. 312015
8. Emergencies/ or Emergency Service, Hospital/ or Emergency Treatment/ 205496
9. ((oncolog* or cancer) adj3 (emergency or emergencies)).tw,kf. 3817
10. 8 or 9. 208391
11. 7 and 10. 275
12. ((emergen* or urgent or urgency) adj4 radiotherap*).tw,kf. 512
13. 3 and 12. 112
14. 11 or 13. 382
15. 14 use medall 102
16. limit 15 to english language 80
17. exp *abdominal cancer/ 14677
18. exp *pelvis cancer/ 7137
19. exp *digestive system cancer/ 1215790
20. exp *urogenital tract tumor/ 649444
21. ((pelvi* or abdom* or gynecol* or ovarian or gastro* or genitourin* or Urogenital or endometr* or cervical or vagina* or prostat*) adj3 (cancer* or neoplasm* or neoplasm*)).tw. 773794
22. or/17-21. 2310498
23. radiotherapy/ or cancer radiotherapy/ or exp *radiotherapy/ 659843
24. (radiation therap* or radiotherap*).tw. 668706
25. 23 or 24. 980743
26. 22 and 25. 208722
27. emergency care/ or emergency treatment/ 129504
28. ((oncolog* or cancer) adj3 (emergency or emergencies)).tw. 3719
29. 27 or 28. 132870
30. 26 and 29. 140
31. ((emergen* or urgent or urgency) adj4 radiotherap*).tw. 512
32. 22 and 31. 77
33. 30 or 32. 214
34. (exp animal/ or nonhuman/) not exp human/ 12647557
35. 33 not 34. 213
36. 35 use emcxd 164
37. limit 36 to English language 149

38. 16 or 37.229
39. remove duplicates from 38. 191

II. Literature search strategy for radiotherapeutic management of bleeding and/or hemorrhage resulting from primary pelvic malignancies.

Embase Classic+Embase <1947 to 2022 June 20>

Ovid MEDLINE(R) ALL <1946 to June 20, 2022>

1. exp abdominal neoplasms/ or exp digestive system neoplasms/ or pelvic neoplasms/ or exp urogenital neoplasms/ 3304465
2. ((pelvi* or abdom* or gynecol* or ovarian or gastro* or genitourin* or Urogenital or endometr* or cervical or vagina* or prostat*) adj3 (cancer* or neoplasm* or malignanc*)).tw,kf. 827926
3. 1 or 2. 3452975
4. exp radiotherapy/ 877944
5. (radiation therap* or radiotherap*).tw,kf. 696184
6. 4 or 5. 1148801
7. 3 and 6. 312182
8. hemorrhage/ or gastrointestinal hemorrhage/ or uterine hemorrhage/ 304325
9. (h?emorrhag* or bleed*).tw,kf. 1258835
10. 8 or 9. 1348801
11. 7 and 10. 10848
12. Palliative Care/ 150439
13. (palliative care or end of life care).tw,kf. or palliative.ti. 133306
14. 12 or 13. 207841
15. 11 and 14. 642
16. 15 use medall 208
17. exp *abdominal cancer/ 14674
18. exp *pelvis cancer/ 7135
19. exp *digestive system cancer/ 1216087
20. exp *urogenital tract tumor/ 649490
21. ((pelvi* or abdom* or gynecol* or ovarian or gastro* or genitourin* or Urogenital or endometr* or cervical or vagina* or prostat*) adj3 (cancer* or neoplasm* or malignanc*)).tw. 799145
22. or/17-21. 2326883
23. radiotherapy/ or cancer radiotherapy/ or exp *radiotherapy/ 659925
24. (radiation therap* or radiotherap*).tw. 668912
25. 23 or 24. 981073
26. 22 and 25. 210767
27. *bleeding/ or abdominal bleeding/ or tumor bleeding/ 110765
28. (h?emorrhag* or bleed*).tw. 1234409
29. 27 or 28. 1258076
30. 26 and 29. 6877
31. cancer palliative therapy/ or *palliative therapy/ 100206
32. (palliative care or end of life care).tw. or palliative.ti. 124695
33. 31 or 32. 163834
34. 30 and 33. 416

35. (exp animal/ or nonhuman/) not exp human/ 12649165
36. 34 not 35. 415
37. 36 use emczd 298
38. 16 or 37. 506
39. remove duplicates from 38. 412