Review Article on Palliative Radiotherapy Column

Appropriateness of the 30-day expected mortality metric in palliative radiation treatment: a narrative review

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Background and Objective: The 30-day expected mortality rate is frequently used as a metric to determine which patients benefit from palliative radiation treatment (RT). We conducted a narrative review to examine whether its use as a metric might be appropriate for patient selection.

Methods: A literature review was conducted to identify relevant studies that highlight the benefits of palliative RT in timely symptom management among patients with a poor performance status, the accuracy of predicting survival near the end of life and ways to speed up the process of RT administration through rapid response clinics.

Key Content and Findings: Several trials have demonstrated substantial response rates for pain and/or bleeding by four weeks and sometimes within the first two weeks after RT. Models of patient survival have limited accuracy, particularly for predicting whether patients will die within the next 30 days. Dedicated Rapid Access Palliative RT (RAPRT) clinics, in which patients are assessed, simulated and treated on the same day, reduce the number of patient visits to the radiation oncology department and hence the burden on the patient as well as costs.

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Conclusions: Single-fraction palliative RT should be offered to eligible patients if they are able to attend treatment and could potentially benefit from symptom palliation, irrespective of predicted life expectancy. We discourage the routine use of the 30-day mortality as the only metric to decide whether to offer RT. More common implementation of RAPRT clinics could result in a significant benefit for patients of all life expectancies, but particularly those having short ones.

Keywords: Palliative radiotherapy; end-of-life; 30-day; mortality; single-fraction; Dedicated Rapid Access Palliative RT (RAPRT) clinics

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Background and objective

Palliative radiation treatment (RT) is recognized to benefit patients with advanced cancer by reducing pain from bone metastases, relieving spinal cord compression, and reducing bleeding (1). Over half of patients with advanced cancer will require RT during their journey (2). Despite palliative RT being efficacious and cost-effective, barriers exist that sometimes prevent its timely application and use (3). One of these is the perception that while palliative RT is highly effective, it takes too long to generate a response for someone with a short life expectancy. As a result, there has been an increasing interest in identifying patients near the end of life and reducing the use of RT in the last few weeks of life (4). The expected 30-day mortality rate has been examined in 42 studies in relation to the use of palliative RT (5). Several groups have proposed using this metric to determine which patients should not receive RT. For example, the Royal College of Radiologists of the United Kingdom has recommended that palliative RT should be administered in no more than 20% of patients expected to die within 30 days of treatment (6). Despite its increasing use and suggested importance in the literature, we contend that the expected 30-day mortality rate for patients should not preclude the decision to administer palliative RT, if relevant symptom relief is expected. Furthermore, there are substantial limits to the accuracy of predictions of patients' life expectancy.

Several clinical trials have confirmed the utility of single fraction radiotherapy (SFRT) for palliative treatment (7). While SFRT uses fractionations of 8–10 Gy with a lower biological equivalent dose (BED) than multi-fraction radiotherapy (MFRT) regimens such as 20 Gy in 5 fractions or 30 Gy in 10 fractions, several published trials and meta-analyses summarizing these results have shown no significant differences in pain response between SFRT and MFRT for patients with bone metastases (8,9). Additionally, using SFRT reduces resource utilization for the healthcare system and decreases the burden of making multiple clinic visits for patients and caregivers when compared to MFRT (10,11).

In this narrative review, we summarize the evidence on the relief of pain caused by bone metastases, the neurologic effects of spinal cord compression, and hemoptysis with SFRT, especially within the first month after treatment. The inaccuracies of survival predictions by clinicians using the 30-day mortality metric could result in under-use of palliative RT, despite the benefits in providing timely symptom management for patients with a poor performance status. Finally, we will discuss the potential for Rapid Access Palliative RT (RAPRT) clinics to administer treatment with short turnaround times and reduced patient visits. We contend that the expected 30-day mortality rate by itself should not preclude giving palliative RT if it is likely to produce symptom relief that is meaningful to the patient. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-56/rc).

Methods

A literature search was conducted using the PubMed and the MEDLINE databases. The analyzed population was adult patients with a known diagnosis of a metastatic solid tumor receiving palliative RT for painful bone metastases, spinal cord compression and hemostasis. Publication inclusion criteria were: randomized and non-randomized controlled trials; prospective and retrospective cohort studies; review articles; and case reports and case series

including patients with metastatic cancer receiving palliative RT, predominantly using a single fraction. We excluded: abstracts, letters and editorial commentaries; outcomes analysis more than 4 weeks after receiving palliative RT; studies using brachytherapy or stereotactic RT; fraction sizes larger than 10 Gy; paediatric populations; and treatment of brain metastases. The main outcome was to review the time to response after a single fraction of palliative RT, prognostic models of survival near the end of life and the implementation of RAPRT clinics.

Key content and findings

Symptom response within four weeks of SFRT

Bone metastases

Trials describing the time to response for patients with bone metastases treated with SFRT are listed in *Table 1*. The complete response rate at four weeks after SFRT varied across studies, ranging from 4% (21) to 40% (23); the rate of having any degree of response at four weeks ranged from approximately 40% (13) to 80% (28).

A few trials have further detailed pain relief in the first few weeks after RT. Steenland *et al.* (26) reported a randomized trial in which 1,171 patients received either 6 fractions of 4 Gy or a single fraction of 8 Gy. Patients completed weekly self-assessment forms documenting pain at the treated site, analgesics consumption, quality of life, and side effects for 3 months after RT. These showed that the average pain score started to decrease as early as week one, and the median time to response was 3 weeks. These findings of early response to palliative RT were confirmed in another study by McDonald *et al.*, in which 41% of patients experienced early pain reduction at day 10 after RT, the same proportion as at day 42 (39%) (15). The reduction of analgesia, mostly opioids, was also an indicator of response. Some publications report a decrease of up to 25% in the first month (18), and the total withdrawal of the drug in 12% of the patients at 4 weeks (27).

Patients undergoing retreatment are also likely to achieve pain response within the first four weeks after treatment. Four retrospective studies described the time to pain relief after re-irradiation to a bone metastasis (*Table 2*). Partial response rates at four weeks ranged from 14% (30) to 72% (31), and complete response rates from 35% (31) to 82% (30). A single randomized trials have also demonstrated the non-inferiority of the SFRT in re-irradiation to bone metastases, compared to MFRT (32).

Despite previous efforts, no one has yet been able to accurately predict which patients will respond to RT for bone metastases. van der Velden *et al.* developed a prediction score for pain response after palliative RT from a study of 452 patients in an effort to identify patients more like to respond to treatment (33). Primary tumor site, performance status, and baseline pain score were found to be predictive of pain response; nevertheless, the authors concluded that it is difficult to predict the likelihood of pain response (33). Similarly Westhoff *et al.* (34) prospectively studied the quality of life in 956 evaluable patients after palliative RT for painful bone metastases, using weekly questionnaires adjusted for primary tumor, for 12 weeks, and then monthly until 2 years. The rate of pain response to RT was 76%. On multivariate analysis, breast and prostate tumor without visceral metastases, good performance status, younger age, and the use of opioids were predictors for response after radiotherapy. However, the developed model for predicting pain response did not have good discriminative power, with a low C-statistic (0.56). Neither study tried to predict response within 4 weeks of RT.

Future efforts research should focus on identifying the appropriate patients who are most likely to benefit from this intervention. Although SFRT is highly cost-effective compared to MFRT, offering this treatment to all eligible cancer patients at end of life, may add additional burden to the healthcare system (11).

Spinal cord compression

Malignant spinal cord compression due to bone metastases or epidural disease can cause pain, numbness, weakness, loss of bowel and bladder sphincter function, and even paralysis, depending on the location, and must be treated as an emergency. Although the median duration of response (5 *vs.* 4.5 months; P=0.4) (35) and the rate of re-treatment was higher with the use of SFRT compare to MFRT (17% *vs.* 4%; P=0.06) (36), both SFRT and MFRT have similar efficacy (37), which has been demonstrated in a few randomized trials (35,36). Time to response to SFRT has been analyzed in three series (35,38,39) (*Table 3*). Pain response after RT was nearly 50% at two weeks (38), and motor function responded in 62% of patients at four weeks after SFRT in another (35). Although the duration of control could be shorter with SFRT, these findings suggest that SFRT results in a relatively rapid response and is as effective in patients with spinal cord compression, underscoring their appropriateness in the poor prognosis population being discussed.

Table 1 Pain relief in treatment of bone metastases after SFRT

Study	Study type	N (single fraction)	Primary cancer site	Location of metastases	Complete response at 4 weeks	Partial response at 4 weeks	Comments
Sit 2022, (12)	Prospective	376 (the entire cohort) and 464 courses of treatments	Breast 100%	Spine 46%; pelvis 31%; lower extremity 9%; upper extremity 6%; rib 5%; skull 1%; other 2%	25.2%	–	PRO questionnaire at 3–4 weeks
Muller 2020, (13)	Prospective	46	Lung 33%; breast 9%; prostate 13%; kidney 11%; thyroid 7%; skin 13%; colon 4%; bladder 2%; esophageal 2%; salivary and parotid adeno 4%; cholangiocarcinoma 2%	Extra-axial 59%; spine 41%	16.1%	38.7%	50% of the patients had at least a partial response 1 week after treatment
van der Velden 2018, (14)	Prospective	432	Prostate 127 29%; breast 97 23%; lung 23%; other 25%	Spine 63%; pelvis 20%; long bones 7%; ribs 3%; other 7%	25%	36%	Median time to response was 4 weeks (range, 1–15 weeks)
McDonald 2017, (15)	Secondary analysis of a randomized trial	298	Prostate; breast; lung; other	Pelvis and hip; spine; limbs; other	12%	28%	At day 10
Conway 2016, (16)	Prospective	531	Genitourinary 33%; lung 21%; breast 25%; gastrointestinal 6%; lymphoma 10%; other 6%	Spine 35%; pelvis 27%; extremity 24%; ribs 10%; other 4%	17%	78%	Patient reported outcomes at 3–4 weeks after RT
Hoskin 2015, (17)	Randomized	325	Breast 34%; lung 34%; prostate 18%; gastrointestinal 6%; kidney 2%; head and neck 2%; bladder 2%; endometrium 0.3%; other 2%	Spine 41%; pelvis 22%; hip 15%; humerus 5%; other 17%	35%	48%	Favor 8 Gy compared to a single fraction of 4 Gy. Retreatment 14%
Gutiérrez Bayard 2014, (18)	Randomized	45	Lung 11.1%; prostate 31.1%; breast 40%; other 17.8%	Limbs 15.6%; axial skeletal 62.2%; cranial 6.7%; multiple 15.5%	17%	62%	Monitoring of patients was performed at 15, 30, 60, 90 days of treatment completion. It was described reductions of analgesia since visit 1. 13.3% underwent re-treatment

Table 1 (*continued*)

Table 1 (*continued*)

Study	Study type	N (single fraction)	Primary cancer site	Location of metastases	Complete response at 4 weeks	Partial response at 4 weeks	Comments
Zeng 2012, (19)	Prospective	386 (243—single fraction)	Breast 25.9%; prostate 25.4%; lung 24.4%; renal cell 5.7%; colorectal 3.9%; bladder 3.6%; pancreas/ gastric 3.4%; others 7.8%	Spine 33.4%; non-spine 66.6%	59%		BPI: all seven items improved in patients after they received radiotherapy in both spine and non-spine treatment sites. No difference between spine *vs.* non-spine metastases
Majumder 2012, (20)	Randomized	31	Breast 19.4%; lung 3.2%; prostate 77.4%	Spine	23.1%	76.9%	Grade of pain was significantly reduced in both the arms after treatment
Meeuse 2010, (21)	Retrospective of a randomized trial	136	Lung 45%; breast 20%; prostate 15%; other 20%	Spine 26%; pelvis 34%; femur 10%; ribs 12%; humerus 4%; other 14%	4%	47%	Median time to response was 2 weeks (range, 1–9). 8% died within the first 2 weeks. All patients completed treatment. 93% did not undergo re-treatment
Foro Arnalot 2008, (22)	Randomized	78	Breast 27%; lung 24%; prostate 24%; myeloma 4%; digestive 13%; other 8%	Pelvis 45%; spine 29%; long bone 10%; other 6%	15%	60%	At 3 weeks. 28% re-treatment
Hamouda 2007, (23)	Randomized	50	Breast 50%; prostate 16%; lung 20%; other 14%	Spine 42%; pelvis 30%; limbs 20%; other 8%	40%	–	28% response at 2 weeks
Wu 2006, (24)	Prospective	109	Breast 39%; prostate 39%; bronchogenic 3%; other 19%	Spine 47%; pelvis 13% extremity 29%; rib/ sternum 11%	17%	72%	BPI questionnaire
van der Linden 2004, (25)	Retrospective of a randomized trial	556	Breast; prostate; lung; other	Spine; pelvis; femur; humerus; ribs; other	14%	71%	Mean time to response was 3 weeks
Steenland 1999, (26)	Randomized	1,171 (579—single fraction)	Breast 40%; prostate 22%; lung 25%; other 13%	Thoracic/lumbar spine 29%; pelvis 34%; femur 9%; ribs 9%; humerus 6%; other 13%	35%	71%	Median time to response was 3 weeks
Nielsen 1998, (27)	Randomized	120	Breast 35%; prostate 38%; lung 13%; other 14%	Dorsal/lumbar spine 47%; pelvis 20%; hip/femur 15%; other 18%	15%	49%	The frequency of pain relief was defined either by a ≥50% reduction in pain on the VAS. At 4 weeks ≥25, ≥50 and ≥75% increases in the VAS QoL 37, 20 and 11%. 20% retreatment

Table 1 (*continued*)

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Study	Study type	N (single fraction)	Primary cancer site	Location of metastases	Complete response at 4 weeks	Partial response at 4 weeks	Comments
Gaze 1997, (28)	Randomized	134	Breast 45%; prostate 19%; lung 18%; other 18%	Upper limb/sternum 25%; spine 28%; pelvis/lower limbs 47%	38.8%	83.7%	10 Gy. The results shown are the better of the scores recorded at the first two follow up visits at 1 week and 1 month after treatment
Salazar 1986, (29)	Prospective	129	Prostate (40%); breast (29%); lung (18%)	Bone—half body irradiation	19%	47%	The HBI pain relief was dramatic with nearly 50% of all responding patients doing so within 48 hours and 80% within one week from HBI treatment

SFRT, single fraction radiation therapy; PRO, professional quality of life scale; RT, radiation therapy; BPI, brief pain inventory; VAS, Visual Analogue Scale; QoL, quality of life; HBI, half body irradiation.

Table 2 Re-irradiation of bone metastases

Study	Study type	N (single fraction)	Primary cancer site	Location of metastases	Complete response at 4 weeks	Partial response at 4 weeks	Comments
Hernanz 2013, (30)	Retrospective	22	Lung 31%; breast 26%; prostate 13%; colorectal 10%; stomach 5%; bladder 5%; skin melanoma 5%; Merkel cell; carcinoma 5%	Bone 59%; visceral 23%; brain 18%	82%	14%	Response to treatment was recorded 4 weeks after radiotherapy with a good response being the complete disappearance or reduction of symptoms greater than 50%
Hamouda 2007, (23)	Randomized	50	Breast 50%; prostate 16%; lung 20%; other 14%	Spine 42%; pelvis 30%; limbs 20%; other 8%	40%	80%	At 2 weeks 20% and 68%
van der Linden 2004, (25)	Retrospective of a randomized study	173	Breast 34%; prostate 21%; lung 28%; other 17%	Spine 22%; pelvis 40%; femur 8%; humerus 7%; ribs 8%; other 15%	63%		Mean time to response was 3 weeks
Jeremic 1999, (31)	Retrospective of a randomized study	135	Breast; prostate; lung; myeloma; kidney; rectum; other	Spine; pelvis/hip; femur; humerus	35%	72%	Median time to response 2 weeks

Table 3 Spinal cord compression

Study	Study type	N (single fraction)	Primary cancer site	Location of metastases	Complete response at 4 weeks	Partial response at 4 weeks	Comments
Giraldo 2017, (38)	Prospective	35	Lung 40%; prostate 5.7%; breast 2.9%; unfavorable histology 51.4%	Spine	–	47%	Significant reduction in pain intensity and mild reduction of opioids were present at 2 weeks. PR at 2 w is 47%
Rades 2015, (39)	Matched-pair study	121	Breast 10%; prostate 20%; myeloma 2%; lung 24%; unknown 15%; other 21%	Spine	17%		Improved motor function
Maranzano 2009, (35)	Randomized	153	Favorable 28%; unfavorable 72%	Spine	27%	25%	62% motor function response

PR, partial response.

Hemostatic radiotherapy

Bleeding from a number of different sites and tumor types have been shown to respond well and often rapidly to palliative RT (40-49), sometimes within 24–48 hours from the treatment (50) (*Table 4*). Overall response rates at four weeks ranged from 19% to 100%, with nearly all greater than 50%. Complete response rates at four weeks were 47% (49) and 73% (45) in the two studies reporting them.

Prognostic models of survival near the end of life

There have been many improvements in systemic therapies in recent years, resulting in increasing life-spans for patients with metastases and an increasing number of patients in need of palliative treatment at some point (51). Prognostic models have been developed to estimate survival length and prevent unnecessary over-treatment, especially in patients near the end of life, such as the three-variable number of risk factor (NRF) score [2008] (52), the TEACHH model [2014] (53), and the Rades model [2019] (54).

The three-variable NRF study (52) analyzed a total of 395 patients who were grouped according to primary cancer site (breast versus non-breast), site of metastases (bone versus non-bone) and Karnofsky Performance Status (KPS) (KPS greater than 60 versus 60 or lower). It successfully but over-optimistically predicted survival probability at three, six, and 12 months (55). The TEACHH model was developed from a study of 862 patients, with the goal of constructing a model predicting survival of less than three months and greater than one year (53). On multivariate analysis, non-breast or non-prostate tumors, older age (greater than 60 years), liver metastases, Eastern Cooperative Oncology Group (ECOG) score of two to four, hospitalizations within three months before palliative RT, and multiple chemotherapy courses prior to palliative RT were all associated with poorer prognosis. Rades *et al.* developed a prognostic model that predicts 12-month survival (54) from a retrospective dataset including 445 patients. They analyzed the radiotherapy regimen and 13 predictive factors including: age, sex, KPS, primary tumor, time interval between primary diagnosis and development of bone or visceral metastases, sites of bone metastases, number of irradiated or non-irradiated metastases, pathological fracture, fractionation of RT, receipt of surgery, systemic treatment, and receipt of a bisphosphonate or Denosumab prior to RT. On multivariate analysis, survival was significantly associated with KPS, primary tumor type, and age. These factors were used to create a prognostic score which allowed patients to be divided into three groups, with respective twelve-month survival rates of 9%, 38% and 72% ($P<0.001$) and median survival times of three, eight, and 24 months.

A recent study by Razvi *et al.* reported that palliative radiation oncologists largely overestimated survival by an average of 19.0 weeks (56). Similar overestimates in survival were reported in a review of 15 studies of advanced cancer patients (57).

RAPRT clinics

Palliative patients can be highly symptomatic and may in some cases experience an oncologic emergency [e.g., spinal

Table 4 Hemostatic radiotherapy

Study	Study type	N (single fraction)	Primary cancer site	Location of metastases	Complete response at 4 weeks	Partial response at 4 weeks	Comments
Sapienza 2019, (40)	Retrospective	21	Gastrointestinal tract; genitourinary; respiratory tract; head and neck; extremities; gynecological		100%		Primary bleeding control after radiotherapy
Lee 2021, (41)	Retrospective	57	Gastric cancer	–	–	75.4%	
Tey 2014, (42)	Retrospective	103	Gastric cancer	–	80.6%		Bleeding
Tey 2007, (43)	Retrospective	33	Gastric cancer	–	54%		Bleeding
Tey 2019, (44)	Retrospective	36	Bladder cancer	–	61%		Bleeding
Aljabab 2017, (45)	Retrospective	67	Bladder cancer	–	73%	16%	Median time to documented complete response from time of radiotherapy initiation was 5.3 weeks (37 days)
Onsrud 2001, (47)	Retrospective	59	Cervix and corpus uteri	–	90%		Bleeding
Adelson 1987, (48)	Prospective	26	Ovarian	–	19.1%		In the entire cohort bleeding decrease in 71.4% and pain in 55%
Halle 1986, (49)	Retrospective	38	Cervix and endometrium	–	47%	24%	Bleeding

cord compression, superior vena cava (SVC) syndrome]. Treatment requires rapid assessment, and without an established and efficient infrastructure, management of symptoms may be delayed (3). The first RAPRT clinics were established in Canada in 1996 (58). Originally established to reduce long wait times for palliative RT (59), its implementation in Toronto was welcomed by referring physicians, especially between community medical oncologists and palliative care consultants (60).

The main objective of an RAPRT clinic is to provide efficient timelines for palliative referrals, especially for cancer patients nearing the end of life, with the purpose of avoiding multiple visits to the hospital. The patient is assessed, simulated, and treated all in the same day, reducing the burden on patients and caregivers from a minimum of three separate appointments (usually on different days) with traditional scheduling practices to a one-day visit. This type of clinic has demonstrated benefits in improving treatment wait times, allowing for improved assessment of this group of patients, and reducing the anxiety, fatigue, and pain experienced by patients due to delayed treatments and excessive hospital visits. RAPRT clinics also promote the use of evidence-based approaches such as greater use of SFRT (61), better control of prophylactic medications (steroid and antiemetic), and a reduction in the duration of inpatient stays (62,63). The benefit of these clinics has been illustrated in a retrospective analysis published in 2014, in which 97% of patients received treatment to painful bone metastases. Of these individuals, 91% received treatment without a need for further investigations, 51% received a single fraction, and only 11% of patients were admitted to hospital (64). Of note, 56% travelled more than 100 km to be assessed, and this clinic was the patient's first specialist appointment 63% of the time.

RAPRT programs have been adopted globally (65), with most published reports coming from centres in Canada (66-69), the United Kingdom (70), Ireland (71), the United States (61,72) Australia (62,73,74), and New Zealand (58). However, RAPRT clinics have been established in a minority of centres, predominantly within public institutions (62). It should be noted that most of them comes from advanced economies, and the adoption of these models in other jurisdictions remains unknown. Some barriers that hinder the implementation of these kind of clinics still are: the subjective perception of patient inconvenience, the logistics of each health system and economic influences (65,75),

geographical considerations/distribution of treatment facilities in the urban and rural settings, and lack of tissue diagnosis at the time of presentation. In addition, countries with insufficient resources may prioritize radical treatments at the cost of palliative RT. Not all eligible patients are referred even in centres where an RAPRT clinic has been established. In one study, only 48% of eligible palliative patients were referred to the RAPRRT clinic, even when they proved that median wait time in the RAPRT was one day from referral to planning, compared to three days for patients referred through the standard pathway of referral (73). However, even if the entire process is carried out in one day, patients should wait approximately 4 hours from the initial evaluation to the start of treatment. This wait can cause reluctance of patients to be treated on the same day.

Conclusions and recommendations

In this article, we review the evidence to question the appropriateness of using 30-day mortality as metric for palliative therapy. Real-world data from a recent meta-analysis on palliative radiotherapy indicate a 16% rate of 30-day mortality from the 42 studies reviewed (5). It has been suggested that the rate of the 30-day mortality be used as a quality indicator for patient selection and appropriate care. However, as we describe in the manuscript, there is sufficient evidence to confirm that SFRT is effective in palliating patients' symptoms even near the end of life, with quick onset of symptom relief, and at least half of the patients clinically benefit from treatment within 30 days.

Additionally, survival estimates by health care professionals are also far from accurate. In short we believe it is unethical to withhold from or not offer palliative RT to patients who may potentially benefit. Patients who are willing and eligible should be offered the opportunity to receive treatment to relieve suffering, due to the fact that palliative RT does help with symptoms even the expectancy life would be less than 4 weeks. Given the benefits of SFRT in managing symptoms and relieving patient burden, protracted MFRT schedules should be avoided in this often frail group of patients. We encourage individualized discussions about the pros and cons of palliative RT between health care professionals and patients, and that expected 30-day mortality should not be used as the sole patient selection criteria, although it may influence the decision making. We also encourage RT centres to adopt the RAPRT clinic model resulting in timely same-day consultation, simulation, and treatment, thereby reducing the patient and caregiver burden of multiple visits to treatment centres.

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