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# Palliative Radiotherapy at the End of Life

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## Abstract

**Purpose:** A significant proportion of patients with advanced cancer undergo palliative radiotherapy (RT) within their last 30 days of life. This study characterizes palliative RT at our institution and aims to identify patients who may experience limited benefit from RT due to imminent mortality.

**Materials and methods:** 518 patients treated with external beam RT to a site of metastatic disease between 2012-2016 were included. Mann-Whitney U and chi-squared tests were used to identify factors associated with RT within 30 days of death (D30RT).

**Results:** Median age at RT was 63 years (IQR 54-71). Median time from RT to death was 74 days (IQR 33-174). 125 patients (24%) died within 30 days of RT. D30RT was associated with older age at RT (64 *vs.* 62 years, p=0.04), shorter interval since diagnosis (14 *vs.* 31 months, p<0.001), liver metastasis (p=0.02), lower KPS (50 *vs.* 70, p<0.001), lower BMI (22 *vs.* 24, p=0.001), and inpatient status at consult (56% *vs.* 26%, p<0.001). Patients who died within 30 days of RT were less likely to have hospice involved in their care (44% *vs.* 71%, p=0.001). D30RT was associated with higher Chow and TEACHH scores at consult (p<0.001 for both).

**Conclusions:** 24% of patients received palliative RT within 30 days of death. Additional tools are necessary to help physicians identify patients who would benefit from short treatment courses or alternative interventions to maximize quality at the end of life.

**Keywords:** Radiation therapy; Palliative care; Predictive tools

## Introduction

More than half of patients treated with radiotherapy (RT) are treated with palliative intent. RT has well-established utility for pain palliation from bone metastases, may be used to improve neurological function or prevent further neurological compromise in patients with brain or spinal cord metastases, and can be used to alleviate symptoms due to obstruction by tumor.

While the response rate to RT in the treatment of bone metastases is high, at approximately 60%, the time frame for symptomatic improvement is typically measured in weeks [1-4]. Palliative RT for brain metastases may result in stable or improved neurologic symptoms in about half of patients, however is also associated with side effects and may not improve overall survival [5-7]. Patients undergoing RT at the end of life may not experience symptomatic benefit and may spend a significant proportion of their remaining life expectancy receiving treatment [8]. Time spent on treatment at the end of life may not align with patients' end of life goals, particularly in the United States where single fraction RT is less commonly utilized. Medicare data suggests that in the United States, almost 8% of patients dying of cancer will receive RT in their last month of life, and almost 20% of these patients will be treated in 10 or more fractions [9,10].

The purpose of this study is to characterize use of palliative RT in patients with advanced cancer at a single institution and identify factors associated with RT within 30 days of death (D30RT).

## Methods

### Patient information

We performed a retrospective review to identify patients who received external beam RT to a site of metastatic disease at the University of California, San Francisco between 2012-2016. Patients treated with stereotactic radiosurgery (SRS) for limited brain metastases were excluded from this analysis as this represents a highly select group of patients; at our institution, each case is reviewed at a weekly multidisciplinary SRS tumor board and the treatment decision takes into account factors such as patient performance status, control of extracranial disease, and potential systemic therapy options. As our patient list was generated using ICD codes for secondary malignant neoplasms (196-198, C78, and C79) listed in our electronic medical record system (MOSAIQ; Elekta; Stockholm, Sweden), we also excluded patients receiving potentially palliative RT to their primary tumor.

Patient characteristics such as age, gender, primary diagnosis, prior chemotherapy or other systemic treatment, performance status at consult, use of hospice services, and radiation dose/fractionation were abstracted from the medical record. In addition to clinical variables used to calculate the TEACHH and Chow scores described below, we

also recorded BMI, as weight loss has been shown to be a poor prognostic sign in patients with cancer, and inpatient status at the time of consult [10,11]. Vital status and date of death were confirmed with our institutional tumor registry. This retrospective review was approved by the institutional review board.

## Prognostic scores

The TEACCH and Chow models have been described previously [12,13]. The Chow model of risk factors grouping is simple to use and categorizes patients based on 3 risk factors: non-breast primary, non-bone metastases, and KPS ≤ 60. Group I includes patients with 0-1 risk factors, Group II with 2 risk factors, and group 3 with all three risk factors [14]. The TEACHH model assigns points based on the following risk factors: non-breast or prostate primary, age > 60, ECOG performance status 2-4, liver metastases, hospitalization within 3 months of palliative RT consult, and 2 or more prior palliative chemotherapy courses [12]. Patients with 0-1 risk factors are categorized in group A, 2-4 risk factors in group B, and 5-6 risk factors in group C.

## Statistics

The Shapiro-Wilk test was used to evaluate normality of continuous variables. Mann-Whitney U and Chi-squared tests were used to compare patients who received RT within 30 days of death (D30RT) and those who did not. D30RT was calculated from the start of RT. Multivariate analysis was used to identify factors associated with D30RT. A two-sided $p<0.05$ was considered significant. Statistics were performed using IBM SPSS, version 24 (SPSS; Chicago, IL).

# Results

518 patients were included in this analysis. The median age at initial diagnosis was 60 years (interquartile range (IQR) 50-68 years) (Table 1).

| Variable | Median (IQR) or % (n, of 518) |
|---|---|
| Age at diagnosis | 60 (50-68) |
| Percent female | 46% (238) |
| **Race** | |
| White | 66% (340) |
| East Asian | 14% (74) |
| African American | 8.7% (45) |
| Southeast Asian | 3.7% (19) |
| Asian NOS | 3.7% (19) |
| Other (includes American Indian, Pacific Islander) | 4.1% (21) |
| Percent Hispanic | 9.1% (47) |
| Survival time since diagnosis (months) | 28 (11-53) |
| **Primary diagnosis** | |
| Lung | 26% (137) |
| Breast | 19% (97) |
| Prostate | 9.7% (50) |
| Renal cell | 5.8% (30) |
| Colorectal | 5.8% (30) |
| Hepatocellular | 3.8% (20) |
| Head and Neck | 3.5% (18) |
| Skin | 3.3% (17) |
| Other* | 23% (119) |
| Metastatic at diagnosis | 49% (254) |
| **Site of metastases** | |
| Brain | 47% (244) |

| | | |
|---|---|---|
| Lung | 55% (284) | |
| Liver | 40% (208) | |
| Bone only | 17% (90) | |
| BMI last course | 24(21-27) | |
| KPS last consult | 60 (50-80) | |
| KPS >70 | 45% (231/511) | |
| Hospitalization within 3 months of RT consult | 58% (289/500) | |
| **TEACHH score**** | **%(n, of 450)** | **Median survival, months (IQR)** |
| 0-1 | 6.2% (32/450) | 6 (2.8-11) |
| 4-Feb | 68% (352/450) | 2.2 (1.0-5.0) |
| 6-May | 13% (66/450) | 1.3 (0.5-2.3) |
| **CHOW model**** | | |
| I | 18% (92/510) | 4.7 (2-11) |
| II | 44% (227/510) | 2.5 (1.0-5.6) |
| III | 37% (191/510) | 1.6 (0.7-2.7) |
| **Hospice involved** | | |
| Yes | 47% (245) | |
| No | 28% (147) | |
| Unknown | 24% (126) | |
| **Place of death** | | |
| Inpatient, acute care | 23% (120) | |
| Home | 29% (151) | |
| Inpatient hospice, non-acute care | 10% (52) | |
| SNF (not hospice) | 1.5% (8) | |
| Unknown | 36% (187) | |

NOTE: * Includes primary cancer of the liver, bile ducts, esophagus, ovary, pancreas, meninges, endometrium, anus, lymph nodes, CNS, and pleura

**Some patients had incomplete information and thus TEACHH or Chow groups could not be calculated (denominators 450 and 510 respectively). Performance status at RT consult was the most commonly missing information, but also hospitalizations within 3 months of RT consult and number of prior palliative chemotherapy courses.

**Table 1:** Patient characteristics.

The median age at final RT course was 63 years (IQR 54-71 years). The median survival time from diagnosis to final RT course was 28 months (IQR 11-53 months). Sixty-six percent of patients (340/518) were Caucasian, while 14% (74/518) were East Asian and 8.7% (45/518) African American. Forty-nine percent of patients (254/518) had metastatic disease at diagnosis. Forty-five percent of patients (231/511) had a KPS>70 at the time of final RT consult; KPS was not recorded at the time of consultation in 8 patients. Fifty eight percent of patients (289/500) were hospitalized within 3 months of RT consult.

The most common primary malignancies were lung (26%, 137/518), breast (19%, 97/518) and prostate (9.7%, 50/518). The most common treatment sites were bone (57%, 293/518) and brain (28%, 146/518) (Table 2).

| Characteristics | Median (IQR) or % (n, of 518) |
|---|---|
| Palliative course # | 1 (1-2) |
| Age at RT | 63 (54-71) |
| Prescribed fractions | 5 (4-10) |
| 1 | 17% (89) |
| 4-Feb | 9.6% (50) |
| 5 | 32% (167) |
| 9-Jun | 3.5% (18) |
| 10 | 34% (177) |
| >10 | 3.3% (17) |
| **Treatment site** | |
| Bone | 57% (293) |
| Brain | 28% (146) |
| Lung | 2.9% (15) |
| Node | 1.7% (9) |
| Other* | 11% (55) |
| Incomplete RT course | 12% (63) |
| Time from start of last RT course to death (days) | 74 (33-174) |
| NOTE: * Includes soft tissue and visceral metastases | |

**Table 2:** Summary of RT.

The median number of palliative chemotherapy regimens prior to RT was 1, though the range was quite large (0-13 regimens) (IQR 0-3 regimens)

The median time from the start of last RT course to death was 74 days (IQR 33-174 days). 125 patients (24%) died within 30 days of RT. D30RT was associated with older median age at initial diagnosis (63 *vs.* 59 years, p=0.002) and at the time of final RT course (64 *vs.* 62 years, p=0.04), shorter interval since diagnosis (14 *vs.* 31 months, p<0.001), liver but not brain or lung metastasis (p = 0.02, 0.43, and 0.06 respectively), lower median KPS at consultation (50 *vs.* 70, p<0.001), lower median BMI (22 *vs.* 24, p=0.001), and inpatient status at consult (56% *vs.* 26%, p<0.001)(Table 3).

| Parameters | D30RT (median (IQR) or % (proportion)**) | D>30RT (median (IQR) or % (proportion)**)) | Chi-squared or p-value |
|---|---|---|---|
| Age at diagnosis | 63 (52-70) | 59 (47-67) | |
| Age at RT | 64 (55-73) | 62 (52-70) | |
| Gender, % female | 42% (52/125) | 47% (184/393) | |
| % Hispanic | 5.8% (7/119) | 11% (40/381) | |
| Survival time (months, diagnosis to RT) | 14 (5-38) | 31 (14-59) | |
| KPS at RT consult | 50 (20-70) | 70 (50-80) | |
| KPS>70 | 27% (33/124) | 51% (198/387) | |
| BMI at RT consult | 22 (IQR 20-25) | 24 (21-27) | |
| Primary diagnosis breast/prostate | 18% (22/125) | 32% (124/393) | |

| | | | |
|---|---|---|---|
| **Treatment site** | | | |
| Bone | 53% (66/125) | 77% (227/393) | |
| Brain | 34% (43/125) | 26% (103/393) | |
| Lung | 4% (5/125) | 3% (10/393) | |
| Other* | 9%(11/125) | 13% (53/393) | |
| Hospitalization within 3 months of consult | 78% (97/125) | 51% (192/375) | |
| Metastatic at diagnosis | 50% (62/125) | 50% (191/388) | |
| **Sites of metastases** | | | |
| Non-bone | 90% (112/125) | 80% (315/392) | |
| Brain | 51% (63/124) | 47% (181/387) | |
| Lung | 62% (78/125) | 53% (206/390) | |
| Liver | 50% (62/125) | 38% (146/386) | |
| Palliative RT course | 1 (1-2) | 1 (1-2) | |
| Prescribed fractions | 5 (3-10) | 5 (4-10) | |
| TEACHH score | 3 (2-4) | 4 (3-4) | |
| **TEACHH Group** | | | |
| A | 1.6% (2/124) | 9% (30/326) | |
| B | 74% (92/124) | 80%(260/326) | |
| C | 24%(30/124) | 11%(36/326) | |
| **Chow Group** | | | |
| I | 3% (5/124) | 23% (87/386) | |
| II | 41% (51/124) | 46% (176/386) | |
| III | 55% (68/124) | 32% (123/386) | |
| Inpatient consult | 56% (70/125) | 26% (103/393) | |
| Hospice involved | 44% (54/122) | 71% (191/270) | |
| NOTE: *Includes soft tissue and visceral metastases | | | |
| **Denominators reflect missing data and thus are not all 125 (D30RT) or 393 (D>30RT) | | | |

**Table 3:** Characteristics of patients and treatment in those who died within 30-days of RT ($D_{30}RT$) and those who did not ($D>_{30}RT$).

D30RT was associated with higher Chow and TEACHH scores at the time of consult (p<0.001 for both). D30RT was associated with a greater likelihood of not completing the prescribed RT course compared to those who lived longer than 30 days following start of RT (42% *vs.* 6%, p<0.001). Despite poor outcomes, patients who died within 30 days of RT were less likely to have hospice involved in their care (44% *vs.* 71%, p=0.001).

Overall, 12% of patients (63/518) did not complete their final RT course. Patients who did not complete radiation were more likely to be inpatients at the time of RT consultation (19% *vs.* 9%, p=0.001) or have been hospitalized within 3 months of RT (16% *vs.* 8%, p=0.005). Patients who did not complete treatment were more likely to have a KPS<70 than those who completed treatment (84% *vs.* 51%, p<0.001). Patients with a BMI<25$^{th}$ percentile were less likely to complete RT than those with a BMI≥25$^{th}$ percentile (62% *vs.* 76%, p=0.02). Patients who did not complete RT were prescribed more fractions than those who completed RT (median 8 *vs.* 5 fractions, p=0.001) and were more likely to be treated for brain than bone metastases (21% *vs.* 11%, p<0.001). The rate of D30RT was not significantly higher in patients treated for brain metastases than bone metastases (42% *vs.* 29%, p=0.13). Patients who did not complete RT had a shorter period from last RT to death compared to those who did complete treatment (median 18 *vs.* 73 days, p<0.001). Patients unable to complete their last RT course were more likely to be in TEACHH group C (24% *vs.* 11%, p<0.001) and Chow group III (55% *vs.* 32%, p<0.001).

Increased hospice enrollment was associated with a longer interval since diagnosis (28 months *vs.* 21 months, p=0.04). Hospice was less likely to be involved when inpatients were evaluated for RT compared to outpatients (31% *vs.* 42%, p=0.02). There was no association between age at diagnosis, age at RT, TEACHH or Chow score, or KPS and hospice involvement. Patients enrolled in hospice were less likely to die in a hospital setting (6.2%) but rather at home (67%) or in a non-acute care inpatient setting (27%, inpatient hospice unit or skilled nursing facility) compared to those not enrolled in hospice (81% in a hospital, 13% at home, 6% non-acute care inpatient) (p<0.001).

## Discussion

Almost one-quarter of patients receiving palliative RT in this series were treated within their last 30 days of life, slightly higher than reported elsewhere, though Ellsworth et al. did find that in a cohort of patients receiving RT for bone metastases, 26% were treated within 30 days of death [8,10,14]. Gripp et al. demonstrated that 15% of patients referred for palliative RT died within 30 days of admission, however this number may be lower than what we observed due to poorer performance status in their cohort (KPS<50 in >90% of patients compared to 25% of patients in our study), in whom RT may have been deferred [8].

Forty-two percent of patients who received RT within 30 days of death in this cohort did not complete their planned RT course, consistent with the literature [15]. Identification of patients who may not benefit from treatment requires physicians to prognosticate, a task that is difficult and often overly optimistic [16,17]. Several tools have been developed to assist in estimating life expectancy. The palliative prognostic index uses palliative performance status, which is strongly correlated with and can be used interchangeably with KPS, oral intake, and clinical symptoms such as dyspnea, delirium, and edema to estimate life expectancy in patients receiving palliative care [18,19], and performs comparably to similar scores that also take into account white blood cell count, lymphocyte percentage, or delirium in cancer patients [20]. A nomogram has also been created that includes time since diagnosis, performance status, albumin, LDH, and lymphocyte count to predict 15, 30, and 60-day survival [21].

These tools, however, do not evaluate prognosis using cancer specific characteristics. The TEACHH score and Chow model are two prognostic tools that have been developed to predict life expectancy in patients with advanced cancer [12,13]. Both take into account KPS and primary diagnosis; the Chow model also incorporates non-bone metastases while the TEACHH score includes prior chemotherapy, recent hospitalizations, and specifically hepatic metastases.

The TEACHH score categorizes patients into three groups (A, B, and C) with distinct survival times from the start of RT (19.9 months, 5 months, and 1.7 months, respectively) [12]. The Chow "number of risk factors" model categorizes patients into three groups (I, II, and III) with median survival times of approximately 15, 6.5, and 2.5 months respectively [14]. In our cohort, median survival was shorter than estimated across all TEACHH and Chow groups (Table 1). This may reflect use of palliative RT earlier in the disease course among the TEACHH cohort, with a shorter time from diagnosis to RT consult (1.8 months, calculated as the sum of time from diagnosis to metastasis and from metastasis to RT consult), compared to 28 months in our cohort. Patients in our cohort were also more likely to have received prior palliative RT than patients in the TEACHH cohort (44% *vs.* 12.5%). Compared to the Chow training set, our cohort had a substantially lower percentage of patients with bone-only metastases (17% *vs.* 29%), which may translate into a more significant disease burden and thus poorer prognosis in our patients.

As only 45% of patients (30/66) in TEACHH group C and 36% of patients (68/191) in Chow group III died within 30 days of RT, the integrated prognostic tools currently available do not appear sufficiently specific to identify patients at risk for imminent death at the time of RT consultation.

In the United States, there is a tendency to prescribe more protracted treatment regimens in patients with longer anticipated survival [22]. Initial concern regarding durability of control following short course RT may have stemmed from higher re-treatment rates seen following single-fraction RT in RTOG 9714 [23], however the Dutch Bone Metastases Study showed that re-irradiation occurred at a higher rate among non-responders and at lower pain scores in the cohort that received single fraction RT compared to the cohort that received multi-fraction RT, despite similar overall response rates, time to, and duration of response [3]. This suggests that higher retreatment rates after single fraction RT may be due to physician views on the safety of retreatment.

A large body of evidence has demonstrated that single fraction RT courses are as effective as more protracted courses with regard to onset of symptomatic improvement, duration of relief, relative proportion of patients experiencing improvement, and subsequent quality of life in patients with bone metastases [1,24,25]. Similarly, overall survival and functional outcomes are similar between shorter and longer RT courses in the treatment of malignant cord compression, though local control may be improved with longer treatment courses [26]. Similarly, while more fractionated schedules may result in improved PFS in patients with brain metastases, several trials have demonstrated no improvement in survival or neurological status [27].

However, a survey of practicing members of the American Society of Radiation Oncology suggests the most common palliative fractionation pattern in the United States remains 30 Gy in 10 fractions; single-fraction treatment is more common among those practicing in Canada, Australia, and New Zealand [28]. In a survey of radiation oncologists practicing within the Veterans Healthcare Administration, physicians who had been in practice for more than 10 years were less likely to offer single fraction RT compared to those with fewer years in practice (63% *vs.* 90%, p=0.01) suggesting there may be shifts in practice patterns over time [29]. Of note, this survey also found that those who had ever worked in private practice were less likely to offer single fraction RT (64% *vs.* 88%, p=0.03), suggesting that practice patterns may be influenced by practice setting.

Patients receiving RT at the end of life are increasingly receiving more advanced treatment modalities, with a decrease in the proportion receiving 2D RT from 75% to 33% from 2000 to 2009 [30]. Use of 3D RT increased from 27% to 59%, and use of IMRT increased from 0% to 6.2% over the same period. As patients live longer with advanced cancer, and potentially receive more palliative RT courses, there may be indications for such techniques, including retreatment or treatment in close proximity to prior fields. However more advanced planning techniques require more planning and quality assurance time, which is already limited for patients with poor prognosis.

When used appropriately, palliative RT in patients with advanced cancer may relieve symptoms and preserve quality of life. Despite the cost of RT, palliative radiotherapy at the end of life may not translate to increased costs of care in patients appropriately referred to hospice [9].

Together this data suggests we may not be optimally caring for patients at the end of life and that there are many questions that still need to be explored in order to optimize timing and dose of palliative radiation therapy for these patients. Development of prognostic models may allow better patient selection in this context, however the current tools available are not specific for patients at risk for death within 30 days of treatment. Earlier integration of palliative care or hospice services may allow patients and physicians to optimally direct treatment at the end of life.

As all patients in this study received palliative RT to a site of metastatic disease, which is generally not available on hospice, our cohort is likely enriched with patients interested in pursing more aggressive treatment options; thus the rate of hospice involvement in our cohort is not representative of practice patterns at our institution or more broadly generalizable. Unfortunately access to palliative RT while on hospice is quite limited, with 1%-3% of patients serviced by hospice agencies receiving RT [31,32]. Pilot programs have been developed to increase access to RT on hospice, however billing for services remains a significant hurdle to implementation, and patient volume described in the literature is limited [33]. Furthermore, maintaining such programs may be resource intensive due to high rates of personnel turnover [34]. Given the median cost for single fraction RT is approximately $1800 (23) and Medicare hospice payment rates may reach $976 for those requiring continuous home care (for the 2018 fiscal year , compared to $193 for routine home care), it may be possible to find a way to make palliative RT economically feasible [33].

This study is limited in that data was obtained retrospectively and may be incomplete, particularly for patients who were seen prior to the transition to electronic medical records or who received care at other institutions. In particular, data regarding prior chemotherapy was quite limited; while we typically had records documenting the regimen, we often lacked the total number of cycles received. Documentation of the specific indication for palliative RT was inconsistent and highly heterogeneous, which made further analysis difficult. Furthermore, due to the retrospective nature of the data, our information regarding symptomatic improvement and quality of life in patients undergoing palliative radiation at the end of life is limited, however warrants further investigation. One study has suggested that in patients receiving palliative RT within 30 days of death, only 26% may experience some measure of palliation of their symptoms [17].

Our findings are also limited in that patients treated at our institution may have more advanced disease than patients seen in the community, especially those enrolled in Phase I trials or seen in the inpatient setting. Additionally, a significant proportion of patients not enrolled in hospice were being followed by palliative care services. We were unable to more thoroughly assess patterns of palliative care referrals or quantify use of palliative care services in this cohort due to changes in referral codes over time. However it is likely that end-of-life and goals-of-care discussions were occurring more often than it would seem solely based on the rate of hospice enrollment.

## Conclusion

A substantial proportion of patients with advanced cancer undergo palliative RT within 30 days of death. Radiotherapy at the end of life must align with patient-directed goals of care, and offer maximal palliation without interfering with other palliative or hospice practices aimed at maintaining quality of remaining life. Further work is needed to design an integrated prognostic tool that can be used to identify patients at high risk for imminent mortality

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