BMC Palliative Care

RESEARCH

Open Access

Outcomes of patients receiving urgent palliative radiotherapy for advanced lung cancer: an observational study

Yang Xu[1,2*], Celestee Trach[1†], Tracey Tessier[1†], Rishi Sinha[1,2] and David Skarsgard[1,2]

Abstract

Background There is considerable variability in the management of patients with advanced lung cancer referred for palliative radiotherapy owing to uncertainties in prognosis and the benefit of treatment. This study presents the outcomes of patients seen in the Fast Track Lung Clinic, an urgent access palliative radiotherapy clinic, and aims to identify factors associated with treatment response and survival.

Methods Consecutive patients with advanced lung cancer seen in the Fast Track Lung Clinic between January 2014 and July 2020 were included. Patients who underwent radiotherapy were contacted beginning 30 days after radiotherapy to evaluate treatment response. Cluster bootstraps were used to compute confidence intervals for treatment response rate. Prognostic factors for treatment response and overall survival were identified using multivariable generalized estimating equations and Cox regression models, respectively.

Results A total of 558 patients were included, of whom 459 (82.3%) consented to palliative radiotherapy for 1053 indications. The overall treatment response rate was 70.0% (95% CI, 65.8-74.2) for indications with follow-up (70.8%). Higher response rates were observed in patients with better ECOG performance status (OR per point, 0.71; 95% CI, 0.55-0.93; $P = 0.01$) and EGFR-mutant non-small cell lung cancer (OR vs wild-type, 2.46; 95% CI, 1.35-4.51; $P = 0.003$), whereas patients treated for neurological symptoms had lower response rates (OR, 0.27; 95% CI, 0.16-0.45; $P < 0.001$). There was no difference in response rate between patients who died within 30 days of starting radiotherapy and those who survived longer (OR, 0.83; 95% CI, 0.42-1.67; $P = 0.61$). Age; ECOG performance status; smoking history; pathology; EGFR or ALK mutation status; and the presence of liver, adrenal, or brain metastases were associated with overall survival.

Conclusions Palliative radiotherapy was effective for patients with advanced lung cancer, although response rates varied by patient characteristics and treatment indication. This study identified prognostic factors for radiotherapy response and overall survival that can inform treatment decisions in this population.

Keywords Lung cancer, Metastatic, Palliative, End of life, Radiotherapy, Response, Survival

[†]Celestee Trach and Tracey Tessier contributed equally to this work.

*Correspondence:
Yang Xu
yang.xu@albertahealthservices.ca
[1] Division of Radiation Oncology, Tom Baker Cancer Centre, 1331 29 Street NW, Calgary T2N 4N2, Alberta, Canada
[2] Department of Oncology, University of Calgary, 2500 University Drive NW, Calgary T2N 1N4, Alberta, Canada

Background

Lung cancer is the second most common cancer diagnosis worldwide and the leading cause of cancer mortality, partly due to the late stage at which most patients are diagnosed. Patients with advanced lung cancer often experience complex symptomatology that can be responsive to palliative radiotherapy, yet limited life expectancy

and the inconvenience of treatment frequently lead them to forego treatment [1, 2].

The Fast Track Lung Clinic at the Tom Baker Cancer Centre was established to improve the accessibility and expediency of palliative radiotherapy for patients with incurable lung cancer. The clinic receives referrals of patients who may benefit from radiotherapy but are not eligible for curative-intent treatment, stereotactic radiosurgery (SRS), or stereotactic ablative radiotherapy (SABR). Patients who consent to radiotherapy undergo CT simulation on the same day of assessment and begin treatment between the same day and four business days later.

Determining the optimal management strategy for each patient is challenging, with options ranging from supportive care alone to protracted radiotherapy regimens intended to achieve enduring local control. Ideally, treatment decisions should be tailored to a patient's life expectancy, particularly for symptoms with strong evidence supporting the efficacy of shorter fractionation schedules [3, 4]. However, difficulties in prognostication, uncertainties in the benefit of treatment near the end of life, an inability to generalize trial findings, and financial considerations have led to widely divergent practices [5–9].

The purpose of this observational study is to characterize the case mix, treatments delivered, and outcomes of patients seen in the Fast Track Lung Clinic. It aims to inform treatment decisions by identifying factors associated with response to radiotherapy and overall survival.

Methods

The study included consecutive patients referred to the Fast Track Lung Clinic between January 1, 2014, and July 31, 2020. Baseline demographic information, date of diagnosis, pathology, stage, sites of metastases, previous therapy, and Eastern Cooperative Oncology Group (ECOG) performance status were recorded at the initial consultation and updated on follow-up visits. Factors that influenced the decision to offer palliative radiotherapy included treatment indication, age, performance status, comorbid conditions, local and distant tumor burden, availability of additional lines of systemic therapy, anticipated treatment toxicities, and patient wishes. All patients who were offered palliative radiotherapy were counseled about the potential risks and benefits of treatment. If a decision is made by the patient to proceed with radiotherapy, then the treatment indication, radiotherapy schedule, and treatment completion status were documented.

Attempts were made to contact patients beginning 30 days after the completion of radiotherapy to evaluate treatment response and identify potential indications for further treatment. If the goal of treatment was to palliate an existing symptom, then the patient was reminded of their description of the symptom prior to radiotherapy, including its frequency, numerical rating or other measure of intensity, and functional impact. The patient was then asked whether the symptom improved, remained stable, or worsened overall. Patients who were treated prophylactically were asked about the development of symptoms that could be attributed to progression at the treatment site. Treatment response was defined as an improvement in the patient's treated symptom if one existed or the absence of new symptoms attributable to disease progression at the treatment site if radiotherapy was given prophylactically.

A proxy with direct knowledge of the patient's status was used to evaluate treatment response when the patient could not be reached. If the patient was deceased at the time of follow-up, the proxy was asked if the patient had reported any response to treatment before their demise.

Provincial electronic medical records were queried until December 31, 2022, to document the date of death of deceased patients. Patients who were not deceased on December 31, 2022, were censored on the date of their last known encounter with the provincial health care system.

Statistical analysis

Descriptive statistics were used to characterize the study cohort, including the subgroup of patients who died within 30 days of starting treatment. To evaluate response to radiotherapy, treatments were considered on a per-indication basis. Treatment indications were clustered by patient to account for within-patient correlation arising from situations in which a patient is given radiotherapy for multiple indications at the same or different times. Confidence intervals on binomial proportions were computed by bootstrapping to account for clusters.

To identify factors associated with response to radiotherapy, generalized estimating equations were used to extend univariable and multivariable logistic regression models in the setting of clustered data [10, 11]. The variables of interest were patient age, sex, ECOG performance status, smoking history, pathology, chemotherapy history, and radiotherapy dose-fractionation scheme. The response of patients who died within 30 days of starting treatment was separately compared to patients who survived longer. Treatment indication was included as a covariate in multivariable analyses.

Kaplan–Meier estimates were used to assess overall survival after the initial consultation. Univariable and multivariable Cox regression models were then used to identify factors associated with overall survival, and logistic regression models were used to identify factors

associated with mortality within 30 days of consultation. The variables that were evaluated were age, sex, ECOG performance status, smoking history, pathology, sites of metastases, and chemotherapy history. ECOG performance status was modelled as a categorical variable owing to a violation of the linearity assumption when modelled as a continuous variable.

All analyses were performed based on intention to treat using an α of 0.05. Statistical computations were completed using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

A total of 558 patients were eligible for analysis with a median time from initial consultation to death or censorship of 3.5 months. The median age at first consultation was 69 years. Functional status was frequently poor; 48.8% of patients presented with an ECOG performance status of 3 or 4. The vast majority of patients (92.5%) had stage IV non-small cell lung cancer (NSCLC) or extensive stage small cell lung cancer (SCLC). The most common sites of metastases were bone (58.2% of patients), lung (36.0%), and brain (20.4%). Median time from diagnosis to first consultation was 21 days, and only a minority of patients had undergone systemic therapy (20.1%) or surgical resection (6.8%) beforehand.

Of the referred patients, 459 (82.3%) consented to palliative radiotherapy for a total of 1053 indications during 752 initial and follow-up assessments. The most common treatment indications were pain (60.5%), shortness of breath (10.4%), brain metastases (7.7%), and cough (5.7%). Radiation was given prophylactically for 4.7% of indications. The most common dose-fractionation schedule was 20 Gy in 5 fractions (58.7%). Radiotherapy was terminated prematurely in 25 patients receiving treatment for 41 (3.9%) indications because of changes in clinical status. Baseline patient and treatment characteristics are shown in Table 1 and Supplemental Table A1, respectively.

Response to treatment

Assessments of treatment response were obtained from 356 (77.6%) patients treated for 746 (70.8%) indications. Proxies provided information on treatment response in 26.9% of indications. The overall response rate to radiotherapy for all indications was 70.0% (95% CI, 65.8–74.2).

Response rates varied by indication (Supplemental Table A2). Patients who received treatment prophylactically had the highest response rate at 84.4%, which compared favourably to that of symptomatic patients at 69.3%, although the difference was not significant in either univariable (OR, 2.39; 95% CI, 0.92–6.23; $P = 0.08$) or multivariable (OR, 2.59; 95% CI, 0.94–7.12; $P = 0.06$) analyses. The lowest response rates were seen in patients treated for symptoms explained by an underlying neurological etiology, including hoarseness secondary to recurrent laryngeal nerve compression (29.4%), symptomatic peripheral nerve or nerve root compression (36.8%), symptomatic brain metastases (49.1%), and symptomatic spinal cord compression (50.0%). A post-hoc analysis showed that neurological symptoms had significantly lower odds of response to treatment compared to non-neurological symptoms on univariable (43.3% vs. 73.4%; OR, 0.28; 95% CI, 0.17–0.45; $P < 0.001$) and multivariable (OR, 0.27; 95% CI, 0.16–0.45; $P < 0.001$) analyses.

ECOG performance status was strongly associated with response to palliative radiotherapy. The response rates of patients with ECOG performance status 0, 1, 2, 3, and 4 were 85.7%, 77.3%, 74.4%, 63.0%, and 50.0%, respectively. Each numerical increase in ECOG performance status was associated with a reduction in response on univariable (OR per point, 0.68; 95% CI, 0.53–0.86; $P = 0.002$) and multivariable (OR per point, 0.71; 95% CI, 0.55–0.93; $P = 0.01$) analyses.

Response rates also varied with pathology. In particular, patients with NSCLC harbouring a targetable EGFR mutation had higher response rates than those with NSCLC but no targetable mutation on univariable (80.8% vs. 67.6%; OR, 2.02; 95% CI, 1.21–3.38; $P = 0.008$) and multivariable (OR, 2.46; 95% CI, 1.35–4.51; $P = 0.003$) analyses.

Female sex was associated with response on univariable (73.9% vs. 65.3%; OR, 1.50; 95% CI, 1.01–2.24; $P = 0.045$) but not multivariable (OR, 1.35; 95% CI, 0.86–2.13; $P = 0.19$) regression. There was no association between age, smoking history, previous chemotherapy use and treatment response. There were also no differences in response between single-fraction and fractionated radiotherapy (Table 2).

Treatment within 30 days of death

Of the 459 patients treated with radiotherapy, 92 patients (20.0%) died within 30 days of starting treatment. These patients received treatment for a total of 157 indications (14.9%); as in the overall population, the most common indications in this subgroup were pain (64.3%), dyspnea (11.5%), symptomatic brain metastases (5.7%), and cough (3.8%).

Assessments of treatment response were obtained for 49 patients (53.3%) treated for 84 indications (53.5%), compared to 73.9% of indications in patients who survived longer than 30 days after the start of treatment (OR, 0.41; 95% CI, 0.25–0.66; $P < 0.001$).

The treatment response rate of patients who died less than 30 days after starting radiotherapy was 60.7% (95%

Table 1 Baseline characteristics of all patients seen in the Fast Track Lung Clinic

Characteristics	Number of patients ($n = 558$)	%
Age, years		
Median (interquartile range)	69 (61–76)	
Sex		
Male	288	51.6
Female	270	48.4
ECOG performance status on first visit		
0	7	1.3
1	105	18.8
2	173	31.0
3	256	45.9
4	17	3.0
Smoking history		
Current smoker within past year	202	36.2
Former smoker	274	49.1
Never smoker	82	14.7
Pathology		
Non-small cell	488	87.5
Small cell carcinoma	38	6.8
Mesothelioma	12	2.2
Not histologically confirmed	20	3.6
Mutation status among non-small cell lung cancers ($n = 488$)		
Targetable EGFR mutation	82	16.8
ALK mutation	4	0.8
No known targetable mutation	402	82.4
AJCC 8th edition stage		
Stage II-III	34	6.1
Stage IV or extensive stage	516	92.5
Not completely staged	8	1.4
Sites of metastases		
Bone	325	58.2
Lung	201	36.0
Brain	114	20.4
Adrenal	95	17.0
Liver	87	15.6
Malignant pleural effusion	84	15.1
Time since diagnosis		
Median, days	21	
≤30 days	344	61.6
31–90 days	56	10.0
>90 days	158	28.3
Previous treatment		
Surgery	38	6.8
Systemic therapy	112	20.1
Cytotoxic chemotherapy or immunotherapy only	77	13.8
Tyrosine kinase inhibitors only	27	4.8
Cytotoxic chemotherapy and tyrosine kinase inhibitors	8	1.4

Abbreviations: ECOG Eastern Cooperative Oncology Group, *AJCC* American Joint Committee on Cancer, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase

Table 2 Association between patient characteristics at the time of radiotherapy and response to treatment

	Univariable model		Multivariable model	
Variable	**Odds ratio (95% CI)**	***P* value**	**Odds ratio (95% CI)**	***P* value**
Age (per year)	0.99 (0.98–1.01)	0.39	0.99 (0.97–1.01)	0.50
Sex				
Male	1 (Reference)		1 (Reference)	
Female	1.50 (1.01–2.24)	0.045	1.35 (0.86–2.13)	0.19
ECOG performance status (per point)	0.68 (0.53–0.86)	0.002	0.71 (0.55–0.93)	0.01
Smoking history				
Nonsmoker	1 (Reference)		1 (Reference)	
Active smoker	1.02 (0.55–1.88)	0.96	1.79 (0.89–3.60)	0.10
Former smoker	1.13 (0.62–2.04)	0.69	1.72 (0.88–3.35)	0.11
Pathology				
NSCLC without targetable mutation	1 (Reference)		1 (Reference)	
NSCLC with targetable EGFR mutation	2.02 (1.21–3.38)	0.008	2.46 (1.35–4.51)	0.003
NSCLC with ALK mutation	0.32 (0.02–5.17)	0.42	0.53 (0.06–4.57)	0.56
Small cell carcinoma	0.70 (0.25–1.95)	0.50	0.93 (0.31–2.83)	0.90
Mesothelioma	1.08 (0.43–2.75)	0.87	1.49 (0.50–4.41)	0.47
Not histologically confirmed	3.36 (0.71–15.85)	0.13	3.11 (0.60–16.22)	0.18
Prior chemotherapy lines, excluding TKIs				
None	1 (Reference)		1 (Reference)	
At least 1	0.87 (0.53–1.43)	0.57	0.76 (0.45–1.29)	0.31
Radiotherapy fractions				
Single	1 (Reference)		1 (Reference)	
Multiple	0.76 (0.45–1.28)	0.30	1.03 (0.60–1.78)	0.92

Abbreviations: ECOG Eastern Cooperative Oncology Group, *NSCLC* Non-small cell lung cancer, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase, *TKI* tyrosine kinase inhibitor

CI, 46.5–74.9). In comparison, the response rate was 71.2% (95% CI, 66.8–75.5) among patients who survived longer than 30 days. There were no significant differences in response rate between patients who died within 30 days and those who lived longer than 30 days on univariable (OR, 0.63; 95% CI, 0.33–1.18; $P = 0.15$) or multivariable (OR, 0.83; 95% CI, 0.42–1.67; $P = 0.61$) analyses.

Overall survival

There were 535 deaths (95.9%) among the 558 patients enrolled in the study. Median survival was 3.5 months from the time of initial consultation (Fig. 1).

On univariable Cox regressions, older age, male sex, poorer ECOG performance status, smoking history, small cell histology, and the presence of metastases involving the liver or adrenal glands were associated with poorer survival, whereas the presence of a targetable EGFR or ALK mutation was associated with superior survival among patients with NSCLC (Table 3; Figs. 2, 3; Supplemental Figures A1-4).

In the multivariable Cox model, increased age continued to be associated with shorter survival (HR per year, 1.02; 95% CI, 1.01–1.02; $P < 0.001$). Each numerical increase in ECOG performance status from 1 to 4 was associated with shorter survival; the same effect was not observed from 0 to 1, but only seven patients had an ECOG performance status of 0. Current smokers (HR, 1.42; 95% CI, 1.06–1.90; $P = 0.02$) or former smokers (HR, 1.38; 95% CI, 1.04–1.83; $P = 0.03$) had poorer prognoses than never smokers. Patients with NSCLC harbouring a targetable EGFR mutation had superior survival to those without a targetable mutation (HR, 0.49; 95% CI, 0.37–0.65; $P < 0.001$). ALK mutations were also associated with better prognosis (HR, 0.21; 95% 0.05–0.85; $P = 0.03$). In contrast, survival was poor for patients with mesothelioma (HR, 2.63; 95% CI, 1.46–4.73; $P = 0.001$). Finally, survival was poorer among patients with metastases to the liver (HR, 1.82; 95% CI, 1.41–2.35; $P < 0.001$), adrenal glands (HR 1.75; 95% CI, 1.38–2.22; $P < 0.001$), and brain (HR, 1.26; 95% CI, 1.00–1.58; $P = 0.048$).

The factors associated with 30-day mortality were largely a subset of those associated with overall survival in the Cox models. On univariable analyses, older age, male sex, poor ECOG performance status, smoking history, small cell histology, and liver or brain metastases

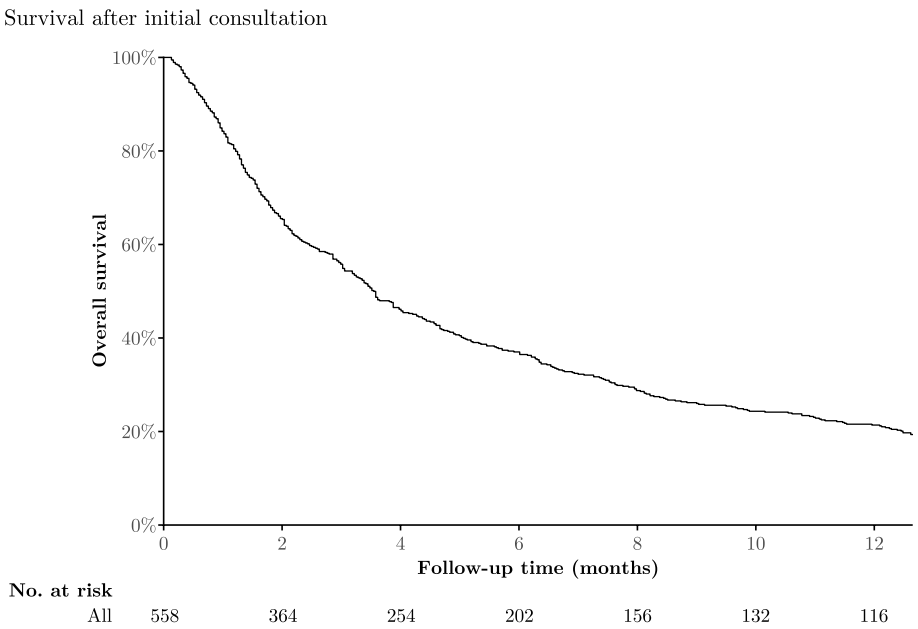


Fig. 1 Kaplan–Meier plot showing the overall survival of all patients referred to the Fast Track Lung Clinic. Median overall survival was 3.5 months

were associated with higher odds of 30-day mortality. By contrast, NSCLC patients with targetable EGFR mutations had lower odds of 30-day mortality. On multivariable analyses, patients with poor ECOG performance status and metastases to the liver or brain continued to have higher odds of 30-day mortality, while targetable EGFR mutations were again associated with lower odds of 30-day mortality in patients with NSCLC (Supplemental Table A3).

Discussion

This large observational study found that palliative radiotherapy effectively treated symptoms associated with advanced lung cancer, even in patients who died less than 30 days after starting treatment. Additionally, we identified prognostic factors for treatment response and overall survival in this population.

While radiotherapy can be effective for all indications examined, response rates varied with treatment indication. The high response rate for prophylactic indications suggests that radiotherapy was effective in preventing the onset of symptoms related to local progression. Importantly, prophylactic radiotherapy was only offered in the Fast Track Lung Clinic to patients expected to become symptomatic imminently. Our findings support the emerging evidence for an expanded role of prophylactic radiotherapy in preventing symptomatic disease progression [12]. However, patient selection remains critical; for instance, no quality-of-life or survival benefits were observed in unselected asymptomatic patients treated with palliative thoracic radiotherapy [13]. Further studies are required to delineate the patients who can benefit from prophylactic treatment in the presence of increasingly effective systemic therapies [14, 15]. A post-hoc analysis in the present study found that neurological symptoms were less likely to improve with radiotherapy. This may stem from the limited capacity of neurons to regenerate, particularly under conditions of chronic injury, and it underscores the need for effective prophylaxis and early detection [16, 17].

Response rates differed significantly depending on patient characteristics. We found that poorer ECOG performance status was associated with a lower response rate, corroborating observations from a recent clinical trial assessing pain response after radiotherapy [18]. A potential explanation could lie in the differences in etiology and complexity of symptoms experienced by patients with poor performance status, rendering them less responsive to treatment [19]. We also found that patients with a targetable EGFR mutation were more likely to benefit from radiotherapy, which may be a consequence of the increased radiosensitivity of EGFR-mutant lung cancer [20]. Clinically, EGFR mutations have been associated with greater responsiveness to cranial irradiation [21], and our study suggests that this may be generalizable to other treatment indications.

Patients who receive radiotherapy near the end of life have historically been poorly studied, likely owing to the difficulties of appropriately timing follow-up. We found that the response rate of patients starting radiotherapy

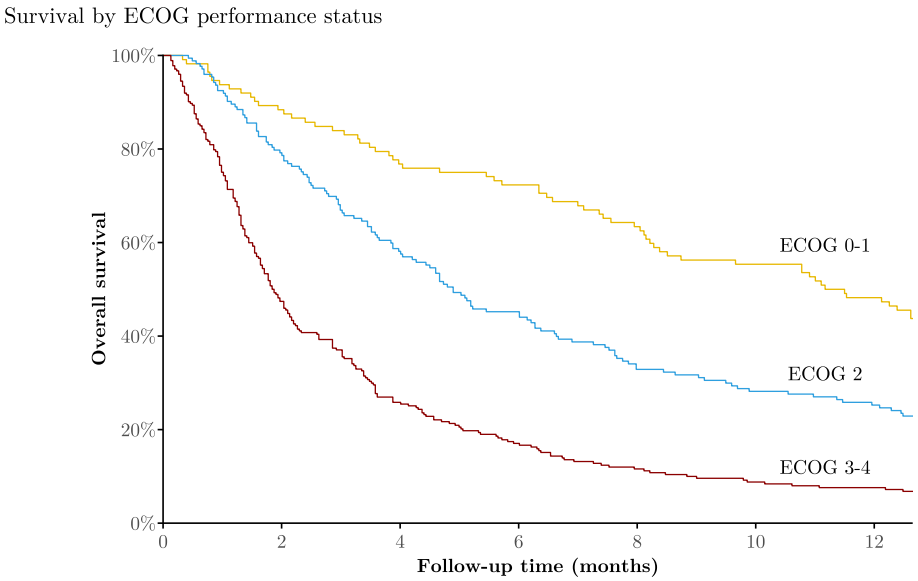
Table 3 Association between patient characteristics at the time of consultation and overall survival

	Univariable model		Multivariable model	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (per year)	1.02 (1.01–1.02)	<0.001	1.01 (1.01–1.02)	<0.001
Sex				
Male	1 (Reference)		1 (Reference)	
Female	0.72 (0.61–0.85)	<0.001	0.85 (0.71–1.01)	0.07
ECOG performance status				
0	0.98 (0.46–2.12)	0.97	0.86 (0.40–1.85)	0.69
1	1 (Reference)		1 (Reference)	
2	1.53 (1.19–1.97)	0.001	1.37 (1.06–1.77)	0.02
3	2.96 (2.33–3.78)	<0.001	2.63 (2.04–3.37)	<0.001
4	13.81 (8.11–23.50)	<0.001	13.75 (7.90–23.94)	<0.001
Smoking history				
Nonsmoker	1 (Reference)		1 (Reference)	
Former smoker	1.85 (1.43–2.39)	<0.001	1.38 (1.04–1.83)	0.03
Current smoker	1.94 (1.49–2.54)	<0.001	1.42 (1.06–1.90)	0.02
Pathology				
NSCLC without targetable mutation	1 (Reference)		1 (Reference)	
NSCLC with targetable EGFR mutation	0.47 (0.36–0.60)	<0.001	0.49 (0.37–0.65)	<0.001
NSCLC with ALK mutation	0.16 (0.04–0.66)	0.01	0.21 (0.05–0.85)	0.03
Small cell carcinoma	1.76 (1.26–2.44)	<0.001	1.29 (0.90–1.85)	0.16
Mesothelioma	1.78 (1.02–3.11)	0.04	2.63 (1.46–4.73)	0.001
Not histologically confirmed	1.54 (0.93–2.54)	0.09	1.34 (0.79–2.26)	0.28
Sites of metastases (present vs absent)				
Liver	1.75 (1.39–2.21)	<0.001	1.82 (1.41–2.35)	<0.001
Adrenal	1.64 (1.31–2.05)	<0.001	1.75 (1.38–2.22)	<0.001
Brain	1.22 (0.99–1.50)	0.06	1.26 (1.00–1.58)	0.048
Lung	1.03 (0.86–1.22)	0.78	1.11 (0.92–1.35)	0.28
Bone	0.96 (0.81–1.14)	0.66	1.11 (0.91–1.34)	0.30
Prior chemotherapy (excluding TKIs)				
No	1 (Reference)		1 (Reference)	
Yes	1.11 (0.88–1.40)	0.39	1.04 (0.80–1.34)	0.77

Abbreviations: ECOG Eastern Cooperative Oncology Group, *NSCLC* Non-small cell lung cancer, *EGFR* epidermal growth factor receptor, *ALK* anaplastic lymphoma kinase, *TKI* tyrosine kinase inhibitor

in the last 30 days of life was not significantly lower than those surviving beyond 30 days, with approximately 60% responding to treatment. The rapidity of benefits experienced by patients in this study aligns with previous studies of longer-lived patients, which have reported response rates exceeding 40% by 10 days and 50% to 60% by one month [22–25]. Importantly, the cognitive and physiological changes in patients near the end of life do not appear to significantly impede patients' ability to respond to treatment. These findings suggest that selected patients near the end of life may still be suitable candidates for palliative radiotherapy.

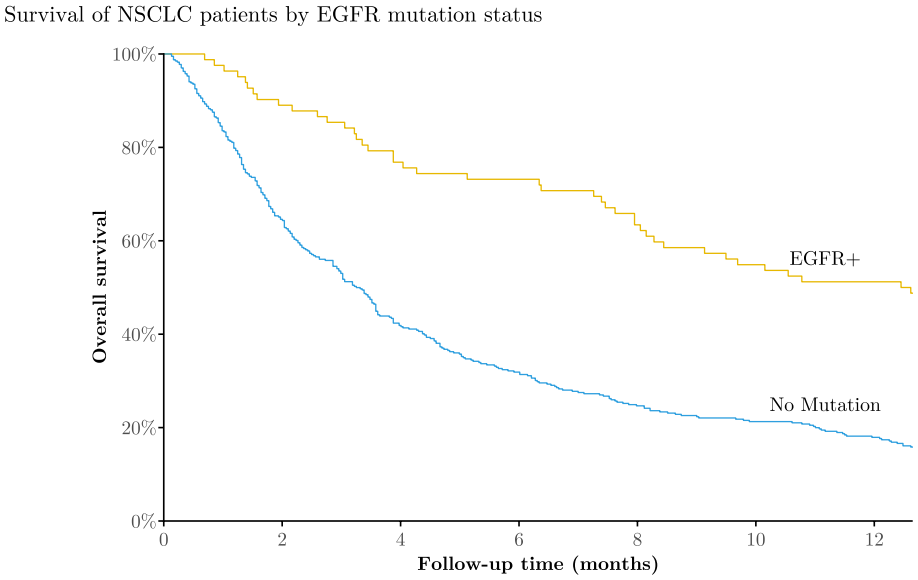
Mortality within 30 days of treatment (TM-30) is a common indicator of poor quality of care in medical oncology [26, 27], and there have been efforts to use this benchmark to identify overly aggressive use of radiotherapy near the end of life. The TM-30 in our cohort was 20%, which is in line with rates of 8% to 24% in the radiotherapy literature [28–35] but considerably higher than most benchmark rates for palliative systemic therapy in lung cancer [27, 36]. However, whereas systemic therapy is unlikely to confer any survival or palliative benefits to patients in their last 30 days of life, our study suggests such patients may still derive a benefit from radiotherapy. As such, an excessively low TM-30 may not be entirely desirable. Furthermore, attempts to lower TM-30 may increase the risk of denying treatment to patients who outlive their life expectancy. Caution is therefore



No. at risk

ECOG 0-1	112	99	86	81	71	62	54
ECOG 2	173	137	99	77	56	48	43
ECOG 3-4	273	128	69	44	29	22	19

Fig. 2 Kaplan–Meier plot comparing overall survival of all referred patients by ECOG performance status



No. at risk

EGFR+	82	73	63	60	52	45	42
No mutation	402	258	165	124	95	82	69

Fig. 3 Kaplan–Meier plot comparing overall survival of non-small cell lung cancer patients with a targetable EGFR mutation (EGFR+) to patients without targetable mutations

warranted in adopting this metric for palliative radiotherapy until studies validating its utility as an indicator for quality of care have been completed.

In addition to concerns about efficacy, travel requirements, treatment expenses, and toxicities have also been cited as barriers to radiotherapy near the end of life [2].

These concerns can be alleviated by shorter courses of radiotherapy, the efficacy of which is well established for several common indications [37–39]. We similarly failed to detect a difference in response rate between single-fraction and multiple-fraction palliative radiotherapy across all indications in this study. Patients near the end of life may be especially suited for single-fraction radiotherapy, wherein the full treatment dose is deposited earlier than in fractionated radiotherapy and concerns about the duration of response are secondary. Additionally, toxicities may be less pronounced in patients treated with single fraction radiotherapy [40, 41]. This contrasts with the frequent use of heavily fractionated radiotherapy schedules internationally [5]. Several contemporary approaches have also shown promise in mitigating the adverse impacts of radiotherapy. Diagnostic imaging-based planning can streamline the planning process and reduce operational costs, while highly conformal radiotherapy including intensity-modulated radiotherapy and particle therapy can potentially improve normal tissue sparing to tilt the benefit-risk balance in favor of treatment in selected patients [42–45]. However, further studies to confirm the safety and cost-effectiveness of these techniques are required to facilitate more widespread adoption.

Reducing the burdens of palliative radiotherapy can be highly consequential, as large swaths of the population with advanced cancer are not currently offered an opportunity for treatment for these very concerns. In a survey of hospices in the United States, fewer than 3% of patients received radiotherapy despite an average stay of 45 days for cancer patients [2, 46]. Further studies emphasizing quality of life are required to identify the patients suitable for palliative radiotherapy near the end of life among the majority who appear to respond positively to treatment.

Our data support the notion that overall survival is limited in this population. Median survival was 3.5 months from the time of consultation, which is consistent with previous reports of patients receiving palliative radiotherapy that ranged from 2 to 9 months [28–30, 47–49]. The short survival is likely explained in part by the advanced disease (92% stage IV or extensive stage) and poor performance status (49% ECOG 3–4) of patients in our study; patients with better prognoses are more likely to be referred for SRS or SABR, which the Fast Track Lung Clinic does not provide.

The difficulties in estimating the longevity of patients referred for palliative radiotherapy can limit the use of shorter fractionation schedules, with previous studies indicating a tendency toward excessive optimism [6–8]. One series on patients receiving radiotherapy within the last 30 days of life found that 84% of estimates of longevity were too optimistic, which may explain why more than 90% of these patients received at most 3 Gy per fraction instead of a more hypofractionated regimen [50]. This highlights the need for a better understanding of factors that predict survival and, ultimately, validated models. Chow et al developed a model stratifying patients referred for radiotherapy into three groups with median survivals of 3, 6, and 12 months based on primary malignancy, Karnofsky performance status, and the presence of extraosseous metastases [51]. The TEACHH model similarly stratified patients into three groups with median survivals of 2, 5, and 20 months using an extended collection of variables, including type of primary tumour, ECOG performance status, age, prior chemotherapy, prior hospitalizations, and the presence of hepatic metastases [52]. A third model focusing primarily on biochemical parameters found that primary lung cancer, peripheral blood neutrophil-to-lymphocyte ratio, plasma urea, and plasma bilirubin were predictive of mortality in the 30 days following palliative radiotherapy [53].

Consistent with the Chow and TEACHH models, we found that age, ECOG performance status, pathology, and the presence of liver metastases were associated with survival in our lung cancer-specific cohort. Our analyses identified additional prognostic factors that may be relevant in this population. We found that patients with NSCLC harbouring targetable EGFR or ALK mutations had markedly longer survival than those without such a mutation, likely reflecting the efficacy of EGFR and ALK tyrosine kinase inhibitors available to most of these patients. On the other hand, patients with mesothelioma had significantly shorter life expectancies, as did current and former smokers compared to never smokers. We also found that adrenal and, to a lesser extent, brain metastases were associated with worse survival. Contrary to the TEACHH cohort, we did not observe an association between previous use of chemotherapy and survival. This may reflect the expanding arsenal of systemic therapies for lung cancer.

The results of our survival analyses can guide patient selection and inform radiotherapy planning. Patients with poor prognoses are typically better suited to hypofractionated radiotherapy, particularly single-fraction treatment, when evidence of efficacy exists for the treatment indication. The subset of these patients whose prognosis is less than 30 days, which this study helped to identify, can be especially challenging. Although we found that selected patients may benefit from radiotherapy, the limited duration of benefit should be weighed carefully against the risk of acute toxicities that may diminish quality of life. Other treatment strategies with fewer short-term toxicities should be considered before the decision to proceed with radiotherapy is made,

although it should be acknowledged that many patients with advanced lung cancer near the end of life are burdened with complex symptomatology that is difficult to control without multimodal therapy [54–56]. Conversely, identification of patients with favorable prognoses may help to select patients who may benefit from dose escalation to achieve prolonged local control and potentially reduce the risk of symptom recurrence [57–59].

To our knowledge, this is the first study that determined treatment response to radiotherapy using proxies when the patient was not reachable. While patient-reported outcomes are the gold standard in measuring symptoms and quality of life [60], they also constrain patient eligibility and elevate the risk of non-response bias. Proxies can be used to overcome these challenges, and they are particularly valuable in providing information about treatment response among patients who are deceased at the time of follow-up, as was the case for patients in our study who died within 30 days of treatment. To minimize the risk of bias arising from proxy responses, answers to the questions posed in this study were designed to be straightforward, observable, and readily communicated by patients to their proxies [61–64]; and we found that response rates were reassuringly in line with the published literature [22–25]. Validation of the use of proxies to assess treatment response is nonetheless warranted in future studies.

There are several other limitations in this study. First, we did not attempt to characterize the severity of patient symptoms or the magnitude and duration of treatment responses, as we were concerned about the reliability of proxies in answering subjective questions [61]. Second, we did not perform adjustments for multiple comparisons. Third, our 30-day mortality analyses were limited by a relatively low event rate; this may help to explain the detection of fewer prognostic factors that influenced survival compared to the Cox models. Lastly, the non-randomized nature of this study is a limitation despite efforts to adjust for patient characteristics; in exchange, the unselected patients in this study are more likely to reflect those seen in day-to-day practice.

Conclusions

This study supports the use of palliative radiotherapy for patients with advanced lung cancer, although predicting which patients will benefit from treatment remains challenging. Ultimately, decisions to offer palliative radiotherapy should account for both likelihood of response and life expectancy. We found that better ECOG performance status, targetable EGFR mutations, and non-neurologic treatment indications were associated with higher response rates to palliative radiotherapy. Response rates were not significantly lower among patients who died within 30 days of starting treatment, suggesting that patients with limited life expectancies still benefit from palliative radiotherapy, if only for a shorter duration. These patients may be better suited to single-fraction treatment, which was not associated with a lower response rate in this study. Prognostic factors for overall survival in this population included age, ECOG performance status, smoking history, pathology, and sites of metastases. These findings can guide patient selection for palliative radiotherapy, although additional studies-particularly those evaluating the magnitude of symptom response and impact on quality of life-are needed to validate our results and more precisely delineate the patients who will derive a net benefit from treatment.

Abbreviations

SRS	Stereotactic radiosurgery
SABR	Stereotactic ablative radiotherapy
ECOG	Eastern Cooperative Oncology Group
NSCLC	Non-small cell lung cancer
EGFR	Epidermal growth factor receptor
ALK	Anaplastic lymphoma kinase
TKI	Tyrosine kinase inhibitor
TM-30	Mortality within 30 days of treatment
OR	Odds ratio
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12904-024-01628-8.

Supplementary Material 1.

Acknowledgements

The authors are grateful for the insights and suggestions provided by Professor Ivo Olivotto during the preparation of this manuscript.

Authors' contributions

Y.X., R.S., and D.S. contributed to the conception and design of this study. C.T., T.T., and D.S. contributed to data acquisition. Y.X. contributed to the analysis and interpretation of data. Y.X. and D.S. contributed to the drafting of this manuscript. All authors critically reviewed the manuscript and provided final approval of the version to be published.

Funding

This research did not receive any funding.

Data availability

The data analyzed in the present study are not publicly available because of privacy restrictions and confidentiality concerns. However, they are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study involved the secondary use of data collected as part of a quality improvement initiative and was approved by the Health Research Ethics Board of Alberta (HREBA) Cancer Committee (IRB No. 00009687), which waived the requirement of informed consent. Data were anonymized prior to analysis. The authors confirm that this study was carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 17 August 2023 Accepted: 16 December 2024
Published online: 21 December 2024

References

1. Hopwood P, Stephens RJ, Bleehen NM, Bolger JJ, Clark PI, Girling DJ, et al. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. Br J Cancer. 1995;71(3):633–6. https://doi.org/10.1038/BJC.1995.124.
2. Lutz S, Spence C, Chow E, Janjan N, Connor S. Survey on use of palliative radiotherapy in hospice care. J Clin Oncol. 2004;22(17):3581–6. https://doi.org/10.1200/JCO.2004.11.151.
3. Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. Pract Radiat Oncol. 2017;7(1):4–12. https://doi.org/10.1016/J.PRRO.2016.08.001.
4. Jumeau R, Vilotte F, Durham AD, Ozsahin EM. Current landscape of palliative radiotherapy for non-small-cell lung cancer. Transl Lung Cancer Res. 2019;8(Suppl 2):S192–201. https://doi.org/10.21037/TLCR.2019.08.10.
5. Fairchild A, Barnes E, Ghosh S, Ben-Josef E, Roos D, Hartsell W, 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. https://doi.org/10.1016/J.IJROBP.2008.12.084.
6. Chow E, Davis L, Panzarella T, Hayter C, Szumacher E, Loblaw A, et al. Accuracy of survival prediction by palliative radiation oncologists. Int J Radiat Oncol Biol Phys. 2005;61(3):870–3. https://doi.org/10.1016/J.IJROBP.2004.07.697.
7. Gripp S, Moeller S, Bölke E, Schmitt G, Matuschek C, Asgari S, et al. Survival prediction in terminally ill cancer patients by clinical estimates, laboratory tests, and self-rated anxiety and depression. J Clin Oncol. 2007;25(22):3313–20. https://doi.org/10.1200/JCO.2006.10.5411.
8. Fairchild A, Debenham B, Danielson B, Huang F, Ghosh S. Comparative multidisciplinary prediction of survival in patients with advanced cancer. Support Care Cancer. 2014;22(3):611–7. https://doi.org/10.1007/S00520-013-2013-2.
9. Koshy M, Malik R, Mahmood U, Husain Z, Weichselbaum RR, Sher DJ. Prevalence and predictors of inappropriate delivery of palliative thoracic radiotherapy for metastatic lung cancer. J Natl Cancer Inst. 2015;107(12):djv278. https://doi.org/10.1093/JNCI/DJV278.
10. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika. 1986;73(1):13–22. https://doi.org/10.1093/BIOMET/73.1.13.
11. Højsgaard S, Halekoh U, Yan J. The R package geepack for generalized estimating equations. J Stat Softw. 2005;15(2):1–11. https://doi.org/10.18637/jss.v015.i02.
12. Gillespie EF, Yang JC, Mathis NJ, Marine CB, White C, Zhang Z, et al. Prophylactic radiation therapy versus standard of care for patients with high-risk asymptomatic bone metastases: a multicenter, randomized phase II clinical trial. J Clin Oncol. 2024;42:38–46. https://doi.org/10.1200/JCO.23.00753.
13. Falk SJ, Girling DJ, White RJ, Hopwood P, Harvey A, Qian W, et al. Immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms: Randomised controlled trial. British Medical Journal. 2002;325. https://doi.org/10.1136/bmj.325.7362.465.
14. Li H, Zhao Y, Ma T, Shao H, Wang T, Jin S, et al. Radiotherapy for extensive-stage small-cell lung cancer in the immunotherapy era. Front Immunol. 2023;14. https://doi.org/10.3389/FIMMU.2023.1132482.
15. Arbour KC, Riely GJ. Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA. 2019;322:764–74. https://doi.org/10.1001/JAMA.2019.11058.
16. Nagappan PG, Chen H, Wang DY. Neuroregeneration and plasticity: a review of the physiological mechanisms for achieving functional recovery postinjury. Mil Med Res. 2020;7:30. https://doi.org/10.1186/S40779-020-00259-3.
17. Patchell RA, Tibbs PA, Regine WF, Payne R, Saris S, Kryscio RJ, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005;366(9486):643–8. https://doi.org/10.1016/S0140-6736(05)66954-1.
18. Ryu S, Deshmukh S, Timmerman RD, Movsas B, Gerszten P, Yin FF, et al. Stereotactic radiosurgery vs conventional radiotherapy for localized vertebral metastases of the spine: phase 3 results of NRG Oncology/RTOG 0631 randomized clinical trial. JAMA Oncol. 2023;9(6):800–7. https://doi.org/10.1001/JAMAONCOL.2023.0356.
19. Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. Support Care Cancer. 2000;8(3):175–9. https://doi.org/10.1007/S005200050281.
20. Anakura M, Nachankar A, Kobayashi D, Amornwichet N, Hirota Y, Shibata A, et al. Radiosensitivity differences between EGFR mutant and wild-type lung cancer cells are larger at lower doses. Int J Mol Sci. 2019;20(15):3635. https://doi.org/10.3390/IJMS20153635.
21. Lee HL, Chung TS, Ting LL, Tsai JT, Chen SW, Chiou JF, et al. EGFR mutations are associated with favorable intracranial response and progression-free survival following brain irradiation in non-small cell lung cancer patients with brain metastases. Radiat Oncol. 2012;7:181. https://doi.org/10.1186/1748-717X-7-181.
22. Truntzer P, Atlani D, Pop M, Clavier JB, Guihard S, Schumacher C, et al. Early evaluation predicts pain relief of irradiated bone metastases: a single-center prospective study. BMC Palliat Care. 2013;12:12. https://doi.org/10.1186/1472-684X-12-12.
23. McDonald R, Ding K, Brundage M, Meyer RM, Nabid A, Chabot P, et al. Effect of radiotherapy on painful bone metastases: a secondary analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol. 2017;3(7):953–9. https://doi.org/10.1001/JAMAONCOL.2016.6770.
24. Saito T, Toya R, Tomitaka E, Matsuyama T, Ninomura S, Oya N. Predictors of pain palliation after radiation therapy for painful tumors: a prospective observational study. Int J Radiat Oncol Biol Phys. 2018;101(5):1061–8. https://doi.org/10.1016/j.ijrobp.2018.04.072.
25. Li KK, Hadi S, Kirou-Mauro A, Chow E. When should we define the response rates in the treatment of bone metastases by palliative radiotherapy? Clin Oncol (R Coll Radiol). 2008;20(1):83–9. https://doi.org/10.1016/J.CLON.2007.09.009.
26. O'Brien MER, Borthwick A, Rigg A, Leary A, Assersohn L, Last K, et al. Mortality within 30 days of chemotherapy: a clinical governance benchmarking issue for oncology patients. Br J Cancer. 2006;95(12):1632–6. https://doi.org/10.1038/SJ.BJC.6603498.
27. Wallington M, Saxon EB, Bomb M, Smittenaar R, Wickenden M, McPhail S, et al. 30-day mortality after systemic anticancer treatment for breast and lung cancer in England: a population-based, observational study. Lancet Oncol. 2016;17(9):1203–16. https://doi.org/10.1016/S1470-2045(16)30383-7.
28. Fraser I, Lefresne S, Regan J, Berthelet E, Chooback N, Ho C, et al. Palliative thoracic radiotherapy near the end of life in lung cancer: a population-based analysis. Lung Cancer. 2019;135:97–103. https://doi.org/10.1016/J.LUNGCAN.2019.02.024.
29. Oorschot BV, Assenbrunner B, Schuler M, Beckmann G, Flentje M. Survival and prognostic factors after moderately hypofractionated palliative thoracic radiotherapy for non-small cell lung cancer. Strahlenther Onkol. 2014;190(3):270–5. https://doi.org/10.1007/S00066-013-0507-Y.
30. Wu SY, Singer L, Boreta L, Garcia MA, Fogh SE, Braunstein SE. Palliative radiotherapy near the end of life. BMC Palliat Care. 2019;18(1):29. https://doi.org/10.1186/S12904-019-0415-8.
31. Spencer K, Morris E, Dugdale E, Newsham A, Sebag-Montefiore D, Turner R, et al. 30 day mortality in adult palliative radiotherapy – a retrospective population based study of 14,972 treatment episodes. Radiother Oncol. 2015;115(2):264–71. https://doi.org/10.1016/J.RADONC.2015.03.023.
32. Walasek T, Sas-Korczyńska B, Dabrowski T, Reinfuss M, Jakubowicz J, Blecharz P, et al. Palliative thoracic radiotherapy for patients with advanced non-small cell lung cancer and poor performance status. Lung Cancer. 2015;87(2):130–5. https://doi.org/10.1016/J.LUNGCAN.2014.11.015.

33. Tiwana MS, Barnes M, Kiraly A, Olson RA. Utilization of palliative radiotherapy for bone metastases near end of life in a population-based cohort. BMC Palliat Care. 2016;15:2. https://doi.org/10.1186/S12904-015-0072-5/.
34. Tseng YD, Gouwens NW, Lo SS, Halasz LM, Spady P, Mezheritsky I, et al. Use of radiation therapy within the last year of life among cancer patients. Int J Radiat Oncol Biol Phys. 2018;101(1):21–9. https://doi.org/10.1016/J.IJROBP.2018.01.056.
35. Kapadia NS, Mamet R, Zornosa C, Niland JC, D'Amico TA, Hayman JA. Radiation therapy at the end of life in patients with incurable nonsmall cell lung cancer. Cancer. 2012;118(17):4339–45. https://doi.org/10.1002/CNCR.27401.
36. Roberts HN, Solomon B, Harden S, Lingaratnam S, Alexander M. Utility of 30-Day Mortality Following Systemic Anti-Cancer Treatment as a Quality Indicator in Advanced Lung Cancer. Clin Lung Cancer. 2024. https://doi.org/10.1016/J.CLLC.2024.04.001.
37. Thirion PG, Dunne MT, Kelly PJ, Flavin A, O'Sullivan JM, Hacking D, et al. Non-inferiority randomised phase 3 trial comparing two radiation schedules (single vs. five fractions) in malignant spinal cord compression. Br J Cancer. 2020;122(9):1315–23. https://doi.org/10.1038/S41416-020-0768-Z.
38. Fairchild A, Harris K, Barnes E, Wong R, Lutz S, Bezjak A, et al. Palliative thoracic radiotherapy for lung cancer: a systematic review. J Clin Oncol. 2008;26(24):4001–11. https://doi.org/10.1200/JCO.2007.15.3312.
39. Chow R, Hoskin P, Schild SE, Raman S, Im J, Zhang D, et al. Single vs multiple fraction palliative radiation therapy for bone metastases: cumulative meta-analysis. Radiother Oncol. 2019;141:56–61. https://doi.org/10.1016/J.RADONC.2019.06.037.
40. Howell DD, James JL, Hartsell WF, Suntharalingam M, MacHtay M, Suh JH, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97–14. Cancer. 2013;119(4):888–96. https://doi.org/10.1002/CNCR.27616.
41. Westhoff PG, Graeff AD, Monninkhof EM, Pree ID, Vulpen MV, Willem J, et al. Effectiveness and toxicity of conventional radiotherapy treatment for painful spinal metastases: a detailed course of side effects after opposing fields versus a single posterior field technique. J Radiat Oncol. 2017;7(1):17–26. https://doi.org/10.1007/S13566-017-0328-1.
42. Louie AV, Granton PV, Fairchild A, Bezjak A, Gopaul D, Mulroy L, et al. Palliative Radiation for Advanced Central Lung Tumors With Intentional Avoidance of the Esophagus (PROACTIVE): A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2022;8:1–7. https://doi.org/10.1001/JAMAONCOL.2021.7664.
43. Glober G, Kubli A, Kielbasa J, Chauhan B, Burch D, Holmes T, et al. Technical Report: Diagnostic Scan-Based Planning (DSBP), A Method to Improve the Speed and Safety of Radiation Therapy for the Treatment of Critically Ill Patients. Pract Radiat Oncol. 2020;10:e425–31. https://doi.org/10.1016/J.PRRO.2020.01.009.
44. Swanick CW, Shang MH, Erhart K, Cabrera J, Burkavage J, Dvorak T, et al. Advancing the Role of Proton Therapy for Spine Metastases Through Diagnostic Scan–Based Planning. Int J Part Ther. 2023;10:85. https://doi.org/10.14338/IJPT-23-00005.1.
45. Lubas MJ, Santos PMG, Yerramilli D, II CBS. Proton therapy in the palliative setting. Ann Palliat Med. 2023;12:1331344. https://doi.org/10.21037/APM-23-230.
46. National Hospice and Palliative Care Organization. 2014 National Summary of Hospice Care. https://www.nhpco.org/archived-national-summary-reports/. Accessed 28 July 2023.
47. Bezjak A, Dixon P, Brundage M, Tu DS, Palmer MJ, Blood P, et al. Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). Int J Radiat Oncol Biol Phys. 2002;54(3):719–28. https://doi.org/10.1016/S0360-3016(02)02989-9.
48. Erridge SC, Gaze MN, Price A, Kelly CG, Kerr GR, Cull A, et al. Symptom control and quality of life in people with lung cancer: a randomised trial of two palliative radiotherapy fractionation schedules. Clin Oncol (R Coll Radiol). 2005;17(1):61–7. https://doi.org/10.1016/J.CLON.2004.09.008.
49. Sundstrøm S, Bremnes R, Aasebø U, Aamdal S, Hatlevoll R, Brunsvig P, et al. Hypofractionated palliative radiotherapy (17 Gy per two fractions) in advanced non-small-cell lung carcinoma is comparable to standard fractionation for symptom control and survival: a national phase III trial. J Clin Oncol. 2004;22(5):801–10. https://doi.org/10.1200/JCO.2004.06.123.
50. Gripp S, Mjartan S, Boelke E, Willers R. Palliative radiotherapy tailored to life expectancy in end-stage cancer patients: reality or myth? Cancer. 2010;116(13):3251–6. https://doi.org/10.1002/CNCR.25112.
51. Chow E, Abdolell M, Panzarella T, Harris K, Bezjak A, Warde P, et al. Predictive model for survival in patients with advanced cancer. J Clin Oncol. 2008;26(36):5863–9. https://doi.org/10.1200/JCO.2008.17.1363.
52. Krishnan MS, Epstein-Peterson Z, Chen YH, Tseng YD, Wright AA, Temel JS, et al. Predicting life expectancy in patients with metastatic cancer receiving palliative radiotherapy: the TEACHH model. Cancer. 2014;120(1):134–41. https://doi.org/10.1002/CNCR.28408.
53. Lee SF, Luk H, Wong A, Ng CK, Wong FCS, Luque-Fernandez MA. Prediction model for short-term mortality after palliative radiotherapy for patients having advanced cancer: a cohort study from routine electronic medical data. Sci Rep. 2020;10:5779. https://doi.org/10.1038/s41598-020-62826-x.
54. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. J Clin Oncol. 2011;29:1151–8. https://doi.org/10.1200/JCO.2010.30.7173.
55. Ford DW, Koch KA, Ray DE, Selecky PA. Palliative and End-of-Life Care in Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST. 2013;143:e498S–e512S. https://doi.org/10.1378/CHEST.12-2367.
56. Hui D, Santos RD, Chisholm GB, Bruera E. Symptom Expression in the Last Seven Days of Life Among Cancer Patients Admitted to Acute Palliative Care Units. J Pain Symptom Manag. 2015;50:488–94. https://doi.org/10.1016/J.JPAINSYMMAN.2014.09.003.
57. Zeng KL, Myrehaug S, Soliman H, Husain ZA, Tseng CL, Detsky J, et al. Mature Local Control and Reirradiation Rates Comparing Spine Stereotactic Body Radiation Therapy With Conventional Palliative External Beam Radiation Therapy. Int J Radiat Oncol Biol Phys. 2022;114:293–300. https://doi.org/10.1016/J.IJROBP.2022.05.043.
58. Nguyen QN, Chun SG, Chow E, Komaki R, Liao Z, Zacharia R, et al. Single-fraction stereotactic vs conventional multifraction radiotherapy for pain relief in patients with predominantly nonspine bone metastases: a randomized phase 2 component of a phase 2/3 trial. JAMA Oncol. 2019;5(6):872–8. https://doi.org/10.1001/JAMAONCOL.2019.0192.
59. Ahn GS, Bruggeman AR, Qiao EM, Moiseenko V, Ray X, Sharabi A, et al. Hypofractionated radiation therapy as palliative management for symptomatic and local control of advanced thoracic malignancies. Ann Palliat Med. 2021;10:10360–8. https://doi.org/10.21037/APM-21-1779.
60. Fabian A, Domschikowski J, Letsch A, Schmalz C, Freitag-Wolf S, Dunst J, et al. Use and Reporting of Patient-Reported Outcomes in Trials of Palliative Radiotherapy: A Systematic Review. JAMA Netw Open. 2022;5:E2231930. https://doi.org/10.1001/JAMANETWORKOPEN.2022.31930.
61. Li M, Harris I, Lu ZK. Differences in proxy-reported and patient-reported outcomes: assessing health and functional status among medicare beneficiaries. BMC Med Res Methodol. 2015;15. https://doi.org/10.1186/S12874-015-0053-7.
62. Takura T, Koike T, Matsuo Y, Sekimoto A, Mutou M. Proxy responses regarding quality of life of patients with terminal lung cancer: preliminary results from a prospective observational study. BMJ Open. 2022;12:e048232. https://doi.org/10.1136/BMJOPEN-2020-048232.
63. Rydén L, Sigström R, Nilsson J, Sundh V, Erhag HF, Kern S, et al. Agreement between self-reports, proxy-reports and the National Patient Register regarding diagnoses of cardiovascular disorders and diabetes mellitus in a population-based sample of 80-year-olds. Age Ageing. 2019;48:513–8. https://doi.org/10.1093/AGEING/AFZ033.
64. Lapin B, Thompson N, Schuster A, Katzan IL. Optimal Methods for Reducing Proxy-Introduced Bias on Patient-Reported Outcome Measurements for Group-Level Analyses. Circ Cardiovasc Qual Outcomes. 2021;14:E007960. https://doi.org/10.1161/CIRCOUTCOMES.121.007960.

Publisher's Note