Development and Validation of a Score Predicting Short Survival (Death within 30 Days) after Palliative Radiotherapy: Better Health Economics and Less Overtreatment

Kent Angelo, Jan Norum, Astrid Dalhaug, Adam Pawinski, Gro Aandahl, Ellinor Haukland, Kirsten Engljähringer, Carsten Nieder

Kent Angelo, Adam Pawinski, Gro Aandahl, Ellinor Haukland, Kirsten Engljähringer, Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway; Astrid Dalhaug, Carsten Nieder, Department of Oncology and Palliative Medicine, Nordland Hospital, Bodø, Norway, and Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway; Jan Norum, Institute of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway, and Department of Oncology, University Hospital of North Norway, 9038 Tromsø, Norway, and Northern Norway Regional Health Authority Trust, Bodø, Norway.

Corresponding author: Carsten Nieder, MD, Department of Oncology and Palliative Medicine, Nordland Hospital, 8092 Bodø, Norway; Tel: +47 75 57 8449, FAX: +47 75 53 4975, e-mail: carsten.nieder@nlsh.no.

Purpose

To develop predictive models that allow for reduced overutilization of palliative radiotherapy (PRT) during the final 30 days of life in patients with incurable cancer.

Patients and Methods

Uni- and multivariate analyses of factors predicting PRT during the final 30 days of life for all PRT courses administered at a dedicated PRT facility between 20.06.07 and 31.12.2009. Development of a predictive model by recursive partitioning analysis (RPA) and independent validation of its performance in patients treated during 2010 and 2011.

Results

We analyzed 579 PRT courses. Median survival was 6.3 months. In 53 cases (9%) PRT was administered during the final 30 days of life. RPA resulted in a model consisting of 6 parameters (low hemoglobin, opioid analgesic use, ECOG performance status (PS) 3-4, known progressive disease outside PRT volume, steroid use, lung or bladder cancer), which correctly identified 75% of PRT courses administered during the final 30 days of life. Maximum survival of patients fulfilling all criteria was 69 days. Death within 40 days occurred in 83%. In the independent validation data set these figures were 74% (30 days), 84% (40 days) and 100% (92 days).

Conclusion

Assigning the right patient to the right palliative approach is challenging. We suggest that patients with lung or bladder cancer and the other adverse features mentioned above are at high risk of dying shortly after initiation of PRT. Our model supports decision making (best supportive care versus PRT) and is the first decision aid specifically addressing PRT near end of life.

Introduction

Accurate, reliable survival estimates in patients with terminal cancer will help both physicians and patients in their decision making. However this task has proven to be a difficult one, often resulting in physicians giving an over-optimistic estimate.[1-3] By combining clinical prediction of survival and objective factors one might hope to improve therapy choices near the end of life in these patients. The aim is to minimize the risk of under- or overtreatment, choosing for example between best supportive care and active cancer treatment, or differently intense therapies.[4] Palliative radiotherapy is often utilized in patients with incurable cancer. Various fractionation regimens exist, which are more or less resource consuming for patients and providers, and which also might carry different toxicity profiles.[5] Therefore, it is important to select wisely. Recent studies indicated that pattern of care are not optimal yet, regarding for example overly aggressive radiotherapy in patients with limited survival due to metastatic malignancies.[6] Improvement of survival prediction strategies is an important area of research. The present study is based on systematically evaluating different clinical and therapeutic baseline parameters, laboratory tests and social factors, and their impact on life expectancy in patients treated with palliative radiation therapy (PRT). The purpose is to give physicians better tools to tailor treatment in patients with terminal cancer receiving PRT.

Methods

Primary endpoint was to establish factors predicting use of PRT during the final 30 days of life. We retrospectively reviewed the records of 412 consecutive patients with metastatic or otherwise incurable cancer receiving PRT at a single hospital with dedicated PRT unit (Nordland Hospital Bodø, Norway (an academic teaching hospital, which is the only provider of oncology services in the county of Nordland)). The patients started their treatment in the time period from 20. June 2007 (date of opening of the dedicated PRT unit) to 31. December

2009. For all patients any additional PRT courses between 1. January 2010 and 1. January 2013 were included in the analyses. Thus, a total of 579 courses were studied (299 patients received only one course of PRT, 78 patients received 2 courses, 24 patients received 3 courses, and 11 patients received 4-6 courses). All medical records, treatment details and information on date of death were available in the hospital's electronic patient record (EPR) system. The survival status and date of death or last follow-up of the patients were obtained from the EPR. Patients who were lost to follow-up were censored on the date of last documented contact (personal appointment, telephone conversation, blood test). Patients who started a new course of PRT after their first one were censored on day 1 of the new course. This was done repeatedly if several PRT courses were administered to the same patient because each course carries a certain risk of being undesirable overtreatment, i.e. PRT during the final 30 days of life. Survival time was measured from day 1 of PRT. We used the Kaplan-Meier method to generate actuarial survival curves and compared these by log-rank test.

We used IBM SPSS (Statistical Product and Service Solutions) Statistics 20 to evaluate the association between PRT during the final 30 days of life and potential predictive factors, including but not limited to primary cancer site, sites of metastases, blood chemistry and hematology parameters, ECOG performance status, age, socioeconomic factors, comorbidity, prescription drug use, smoking status, and various treatment related factors. Univariate analysis consisted of Pearson chi-square and Fisher's exact test. Factors achieving statistical significance (defined as $p < 0.05$ throughout this study, two-sided tests) were entered into multivariate analysis (logistic regression). Independent predictive factors confirmed in multivariate analysis were used to create a score predicting utilization of PRT during the final 30 days of life. We followed the method previously described by Rades et al.[7-9] In brief, the

score for each predictive factor was determined by dividing the rate of PRT during the final 30 days of life (given as the percentage) by 10. The total score represented the sum of the scores for each predictive factor. We also examined a previously described survival prediction score based on three variables (non-breast cancer, metastases other than bone, and Karnofsky performance status (KPS) ≤60 (converted from ECOG performance scale)) for its ability to predict PRT during the final 30 days of life.[10] Because of unsatisfactory results obtained with score-based approaches we performed recursive partitioning analysis (RPA) to develop a better model predicting PRT during the final 30 days of life.[11-13] This is a method of building decision trees to model predictors. All variables with significant p-value in univariate analysis were examined for the best split for our series of 579 PRT courses. Each splitting resulted in the definition of subgroups with high likelihood of having received PRT during the final 30 days of life. Independent validation of RPA results was performed in a patient cohort that received PRT between 01. January 2010 and 31. December 2011 at the same institution (consecutive new patients).

Results

The majority of all 579 PRT courses were given to male patients (61%). Median age was 70 years (range 31-97 years). Prostate (25%) and non-small cell lung cancer (NSCLC, 18%) were the most common diagnoses. Median time interval from first cancer diagnosis to PRT was 27 months (range 1-386 months). Median time interval from first metastasis if any to PRT was 5 months (range 0-149 months). Most patients had progressive disease outside the PRT target volume (60%). Additional baseline information is shown in Table 1. Bone metastases were the prevailing target for PRT (54%). Emergency treatment was given to patients with metastatic spinal cord compression (MSCC, 10%) and superior vena cava compression (SVCC, 2%). The most common PRT regime consisted of 10 fractions of 3 Gy

(36%). Other common regimes included 8 Gy single fraction (bone metastases), 2 fractions of 8.5 Gy (lung cancer), and 5 fractions of 4 Gy (various). Use of more than 15 fractions was uncommon (4%). Few courses included fraction doses <3 Gy (10%). Twenty-five PRT courses (4%) remained incomplete, typically because of clinical deterioration. Median survival from PRT was 6.3 months (Figure 1).

In 53 cases (9%) PRT was administered during the final 30 days of life. In univariate analysis, 19 factors were significantly associated with this endpoint (Table 1). These included ECOG performance status, primary tumor site, known liver metastases, pleural effusion, progressive disease outside PRT target volume(s), hypercalcemia, low hemoglobin, leukocytosis, c-reactive protein level, serum creatinine, oxygen treatment, opioid analgesics, steroid treatment, blood transfusion, Charlson comorbidity index, number of prescription drugs, intended number of PRT fractions, dose per fraction, and incomplete PRT. The last 3 factors were related to PRT prescription and realization. Whether or not PRT can be completed as planned is not known when starting treatment. Dose prescription and number of fractions are influenced by baseline prognostic factors such as performance status. As one might expect, these PRT-related factors were not significant in multivariate analysis.

Multivariate analysis confirmed ECOG performance status, primary tumor type, liver metastases, known disease progression outside the actual PRT target volume(s), steroid use, serum hemoglobin, c-reactive protein and albumin levels as independent predictors for use of PRT in the final 30 days of life (Table 2). The single most important factor was ECOG performance status 3 (relative risk 13.1) or 4 (relative risk 27.8). Twenty-two percent of patients with ECOG performance status 3 and 47% of patients with ECOG performance status

4 received PRT during the final 30 days of life. Other important risk factors, i.e. relative risk >5, were low albumin and high c-reactive protein level.

Predictive score

We used all significant predictors confirmed in multivariate analysis to develop a predictive score. The method has been described by Rades et al.[7-9] For example, patients with ECOG 0-2 were assigned 0 points, those with ECOG 3 2 points (rate of PRT (22.2) divided by 10), and those with ECOG 4 5 points. The results were derived from 330 PRT courses with complete information on all essential parameters. As stated in Table 1 not all information was available in each case. Table 3 shows the resulting sum score (minimum 1, maximum 24 points). Obviously, the risk of PRT during the final 30 days of life was minimal as long as the sum score was 10 or lower. The risk was substantial with sum scores of 18 or higher. However, sensitivity of this score was not optimal. Moreover, one would withhold PRT in only 16 of 330 cases (5%) when basing this decision on sum scores of 18 or higher, a suboptimal number given that 9% of all PRT was administered during the final 30 days of life.

Prediction based on the three variable survival prediction score (SPS, originally described by Chow et al: non-breast cancer, metastases other than bone, and KPS ≤60)[10]

We used different methods of converting ECOG into KPS ≤60 (ECOG 2-4 or ECOG 3-4). A third approach assigned different point sums to ECOG 2 and ECOG 3-4. Irrespective of method SPS significantly predicted survival (Kaplan-Meier curves not shown, $p<0.001$). However, the hypothesis that PRT rate during the last 30 days of life in the most unfavorable group (non-breast cancer, metastases other than bone and poor performance status) would be so high that these patients should not be offered PRT was not valid. In none of our three SPS scenarios more than 29% of patients with poor SPS features died within 30 days.

Prediction based on recursive partitioning analysis

Due to the limitations mentioned above, an alternative approach was explored, namely RPA. As shown in Figure 2 the single most important factor that characterized patients who received PRT during the final 30 days of life was the presence of primary lung or bladder cancer, irrespective of histology. These patients had a median survival of 3.6 months. The most important factor splitting the group with lung or bladder cancer into those with PRT during the final 30 days of life vs. earlier (appropriate) PRT was hemoglobin level below normal limit. However, these two factors were not sufficient for clinical decision making as sensitivity was too low. Even after including the next two factors (opioid analgesics and ECOG performance status) results were not satisfactory (sensitivity 58%, 31 of 53 courses of PRT during the final 30 days of life were predicted correctly). The final model included 6 parameters (lung or bladder cancer, low hemoglobin, opioid analgesic use, ECOG 3-4, known progressive disease outside PRT target volume(s), steroid use), which were not completely identical to those used in the score approach (shown in Table 2). The model correctly identified 75% of PRT courses administered during the final 30 days of life, i.e. performed better than the score approach. Maximum survival of patients fulfilling all criteria was 69 days. Death within 40 days occurred in 83%. Comparable to the score approach, relatively few patients (4%) would avoid inappropriate PRT.

Validation of the predictive model

The independent validation data set included all consecutive patients with lung or bladder cancer who received PRT between 01. January 2010 and 31. December 2011 at the same institution. Overall, 129 courses of PRT were evaluated (105 NSCLC, 14 SCLC, 10 bladder cancer). Twenty-two of these were administered during the final 30 days of life (17%, compared to 16.5% in patients treated before 2010, $p>0.1$). Median age was 66 years (range

41-90 years). ECOG performance status was 0-2 in 91 cases (3 in 25 and 4 in 13 cases, respectively). Progressive disease outside PRT target volume(s) was found in 83 cases and low hemoglobin in 74. Steroids were used in 91 and opioid analgesics in 79 instances, respectively. Median survival after PRT was 3.5 months. Nineteen PRT courses (15%) were given to patients with 6 adverse features (lung or bladder cancer, low hemoglobin, opioid analgesic use, ECOG 3-4, known progressive disease outside PRT target volume(s), steroid use). Of these 19 patients, 14 died within 30 days (74%). Death within 40 days occurred in 84%. Maximum survival was 92 days. These figures were not significantly different from those obtained in the original data set (75% died within 30 and 83% within 40 days, respectively).

Discussion

Estimating life expectancy in patients with advanced cancer has proven to be difficult. Finding objective criteria which physicians can rely on is therefore of critical importance. By defining reliable objective criteria and developing predictive models one hope to correct the over/under-treatment in this patient group. Thereby giving patients better quality of information and a basis for making their own decisions on how they want to spend the last period of their life. In a recent study from Italy, 36% of patients who were admitted in an oncology ward due to acute conditions and died within 4 weeks were on active treatment.[14] In the present study, attempts were made to develop a predictive model that might facilitate decision making for patients referred to PRT. It is clear from previous studies that non all patients benefit from PRT, in part because their survival is too limited to experience symptom relief, which often develops slowly over several weeks.[4, 15] Avoiding futile PRT saves resources, both from a patient and provider perspective. Since many countries have seriously limited health care resources and waiting lists for radiotherapy, avoiding unnecessary PRT

might improve overall cancer care. Comparable to other studies, we chose to focus on the final 30 days of life, although other definitions of short survival and other measures of futility exist.

Disadvantages of our retrospective study design and database include the facts that patient numbers were limited, especially regarding subgroups, and that most patients were elderly (median age 70 years). Data on potentially predictive cancer-related symptoms such as cachexia or dyspnea were not available for analysis. However, we had access to a large number of variables from a consecutive patient population, representative of everyday PRT practice in most developed countries (including emergency PRT and incomplete PRT courses). Stereotactic radiotherapy was not included in the present series. The majority of PRT courses consisted of hypofractionated regimens, mostly 1-15 fractions, with dose/fractionation parameters reflecting a patients' expected prognosis (clinical estimate). We did not use any particular prognostic models or scores when assigning treatment regime. As evident from Table 1, patients who died within 1 month typically were treated with less than 10 fractions and at least 4 Gy per fraction. In other words, less time and resource consuming radiotherapy schedules were preferred. We did not evaluate cause of death in our patient population.

In principle, our results indicate that predictive scores might have some value regarding the endpoint of PRT during the final 30 days of life. However, their accuracy was not fully satisfactory and readers must also be aware that all score or RPA related results are based on 330 PRT courses (incomplete information in the remaining cases). The main reason for not recommending scores being that withholding PRT in all patients with unfavorable prognosis would prevent more than 30% from receiving potentially useful symptom palliation. Our RPA

based decision approach that resulted in 6 predictive parameters (low hemoglobin, opioid analgesic use, ECOG performance status (PS) 3-4, known progressive disease outside PRT volume, steroid use, lung or bladder cancer) was more accurate and appears clinically applicable due to its lower risk of withholding PRT. However, it is applicable only to patients with primary lung or bladder cancer. These patients had median survival of 3.6 months and constituted 29% of all PRT activity. Although the RPA model was not 100% accurate, it was valid in an independent data set.

Over the time period of our study (4.5 years including our validation data set) we found no decrease in utilization of PRT during the final 30 days of life. Overall 9% of all PRT courses were administered in patients with such limited survival. Gripp et al. found that poor performance status, shortness of breath, and brain metastases predicted for survival of less than 1 month.[14] Out of 216 patients referred for PRT in their study 33 (15%) died within 1 month.

References

1. Parkes CM: Accuracy of predictions of survival in later stages of cancer. BMJ 2:19-31, 1972

2. Gripp S, Moeller S, Bölke E, et al: Survival prediction in terminally ill cancer patients by clinical estimates, laboratory test, and self-rated anxiety and depression. J Clin Oncol 25:3313-3320, 2007

3. Glare P, Virik K, Jones M, et al: A systematic review of physicians' survival predictions in terminally ill cancer patients. BMJ 327:195-198, 2003

4. Nieder C, Norum J, Dalhaug A, et al: Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. Clin Exp Metastasis epub ahead of print, 2013

5. van Oorschot B, Rades D, Schulze W, et al: Palliative radiotherapy - new approaches. Semin Oncol 38:443-449, 2011

6. Chen AB, Cronin A, Weeks JC, et al: Palliative radiation therapy practice in patients with metastatic non-small-cell lung cancer: a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Study. J Clin Oncol 31:558-664, 2013

7. Rades D, Dunst J, Schild SE: The first score predicting overall survival in patients with metastatic spinal cord compression. Cancer 112:157-161, 2008

8. Rades D, Dunst J, Schild SE: A new scoring system to predicting the survival of patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol 184:251-255, 2008

9. Rades D, Rudat V, Veninga T, et al: A score predicting posttreatment ambulatory status in patients irradiated for metastatic spinal cord compression. Int J Radiat Oncol Biol Phys 72:905-908, 2008

10. Chow E, Abdolell M, Panzarella T, et al: Predictive model for survival in patients with advanced cancer. J Clin Oncol 26:5863-5869, 2008

11. Cook EF, Goldman L: Empiric comparison of multivariate analytic techniques: advantages and disadvantages of recursive partitioning analysis. J Chronic Dis 37:721-731, 1984. Erratum in: J Chronic Dis 39:157, 1986

12. Gaspar L, Scott C, Rotman M, et al: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37:745-751, 1997

13. Nieder C, Nestle U, Motaref B, et al: Prognostic factors in brain metastases: should patients be selected for aggressive treatment according to recursive partitioning analysis (RPA) classes? Int J Radiat Oncol Biol Phys 46:297-302, 2000

14. Numico G, Occelli M, Russi EG, et al: Survival prediction and frequency of anticancer treatment in cancer patients hospitalized due to acute conditions. Role of clinical parameters and PaP score. Support Care Cancer 19:1823-1830, 2011

15. Gripp S, Mjartan S, Boelke E, et al: Palliative radiotherapy tailored to life expectancy in end-stage cancer patients: reality or myth? Cancer 116:3251-3256, 2010