Title

Usefulness of the Palliative Prognostic Index in Patients with Lung Cancer

Authors

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Introduction

Accurate survival prediction is important for terminally ill patients with advanced cancer to avoid unnecessary anti-cancer therapies and provide appropriate palliative care [1, 2]. However, it is difficult to predict the prognosis in these patients. The Research Network of the European Association for Palliative Care identified performance status (PS), cancer anorexia-cachexia syndrome, dyspnea, delirium, leukocytosis, lymphopenia, and high C-reactive protein as some of the predictors of life expectancy in this patient population [2]. Moreover, a number of prognostication tools, including the Palliative Prognostic Score (PaP score) [3], the Palliative Prognostic Index (PPI) [4], and the Japan Palliative Oncology Study-Prognostic Index (JPOS) [5] have been developed to obtain a rapid estimate of life expectancy. PPI, which is based on assessment of the Palliative Performance Scale (PPS) [6], oral intake, dyspnea at rest, edema and delirium, was developed by assessing patients admitted to the palliative care unit, and has since been successfully validated in a variety of clinical settings, such as acute care hospital and home care settings [7-10]. Although it has been pointed out that PPI is inferior to the PaP score and JPOS for

predicting long-term survival, it has the advantage of being a simple tool for predicting short-term survival without blood examinations [5].

Lung cancer is the leading cause of cancer-related death worldwide, and was estimated, as of 2008, to be responsible for 1.38 million deaths annually [11]. Therefore, it is important to identify prognostication tools for advanced lung cancer patients. Previous studies carried out to evaluate the usefulness of PPI, however, patients with lung cancer accounted for only 6.9%-25.8% of the study populations [7-10]. Lung cancer can be divided into two categories: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC); SCLC has a more aggressive disease course than NSCLC [12]. It remains unclear whether PPI is equally applicable to lung cancer patients with NSCLC and SCLC, who show different clinical courses. We conducted a retrospective study to evaluate the usefulness of PPI for short-term survival prediction in patients with lung cancer. In addition, we compared the usefulness of PPI as a prognostic tool in lung cancer patients with SCLC and NSCLC.

Methods

Patient selection and evaluation

We retrospectively reviewed the clinical data of patients with lung cancer. The inclusion criteria were; 1) patients with cytologically or histologically confirmed diagnosis of lung cancer, 2) who were admitted to our hospital to receive palliative care, and 3) whose death confirmed between 2009 and 2013. The exclusion criteria were; 1) history of anti-cancer therapy, including surgery, radical irradiation, brain irradiation, or chemotherapy after admission, 2) absence of detection of recurrence after radical surgery or radiation therapy, 3) admission to the hospital mainly for acute illnesses such as infection, tumor hemorrhage, or adverse effects of treatment, and 4) apparent death from other causes than lung cancer. Patients who received palliative irradiation were included.

We determined PPI based on the information recorded in the clinical charts at the last admission to our institution. The index was calculated by summing the scores assigned for each of the factors of PPS, oral intake, dyspnea at rest, edema, and delirium (Table 1). The PPS measures physical performance and is measured in 10% decrements, from fully ambulatory and

healthy (100%) to death (0%) [6]. Clinical information, such as the age, gender, histological diagnosis, epidermal growth factor receptor (EGFR) gene status, and Eastern Cooperative Oncology Group PS at admission were also reviewed. The study was approved by the Ethics Committee of the University of Toyama.

Statistical analysis

Survival curves were drawn by the Kaplan-Meier method. Survival was calculated from the date of admission to the date of death. Survival was compared by the log-rank test between patients with PPI values of ≤ 6 and those with PPI values of > 6. Multivariate analysis was performed using the Cox proportional hazards model, with adjustments for the age, gender, histological diagnosis, and EGFR gene status. The sensitivity and specificity of a PPI of > 6 for predicting death within three weeks was evaluated. In addition, we also evaluated the association between PPI and the survival time, and the sensitivity and specificity of PPI for predicting the short-term survival separately in patients with NSCLC and SCLC.

Results

The date of death could be confirmed in 165 patients with lung cancer between 2009 and 2013. Of these, 49 had received anti-cancer treatment after the last admission to our hospital, 24 patients were admitted for acute illnesses, 5 patients showed no recurrence after radical surgery or chemoradiation therapy, and 3 patients apparently died of causes other than lung cancer. Finally, we included the data of 84 patients, including 67 patients with NSCLC and 17 patients with SCLC.

Table 2 shows the patient characteristics. The median (range) age was 72.5 (45-88) years and 74 (88.1%) were male. There were 4, 23, 40 and 17 patients with a PS of 1, 2, 3 and 4, respectively.

Figure 1 shows the Kaplan-Meier curve for the two groups divided according to the PPI using the cutoff level of 6. The group with a PPI of > 6 showed a significantly shorter survival time than that with a PPI of ≤ 6 ($P < 0.0001$). The sensitivity and specificity of PPI determined using the cutoff level of 6 for less than three weeks' survival were 61.3% and 86.8%, respectively. Table 3 shows the association between each of the examined variables and the survival as assessed by the Cox proportional hazards

model. The analysis identified PPI ($P < 0.0001$) and histological diagnosis ($P = 0.011$) as being independently associated with the patient survival.

Figure 2 shows the association between PPI and survival in patients with NSCLC and SCLC. A significant association was detected in both populations, and the sensitivity and specificity of PPI determined using the cutoff value of 6 for predicting less than three weeks' survival were 66.7% and 87.0% for patients with NSCLC, and 50.0% and 85.7% for patients with SCLC, respectively.

Discussion

The present study revealed a close association between PPI and survival in terminally ill patients with lung cancer, and the association was maintained even after the patients were divided into NSCLC and SCLC groups. The index showed a high specificity for prediction of less than three weeks' survival, while the sensitivity was relatively low, especially in patients with SCLC.

PPI was first developed by assessment of patients in palliative care units, and subsequently, its ability for prognostication was validated in a variety of

clinical settings [7-10]. The sensitivity of 61.3% determined in the present study was consistent with previous reports [7, 9, 10], although it decreased to 50% when the analysis included only patients with SCLC. The lower sensitivity in patients with SCLC likely reflects the aggressive nature of SCLC. Some patients with SCLC showed rapid deterioration even if the value of PPI on the day of admission was ≤ 6. Arai et al. reported that measurement of the change of PPI is useful for predicting the survival in patients with advanced cancer [13]. They suggest that it is necessary to not only consider the value of PPI at a single time point, but also the disease history and change of the general status during the clinical course.

The present study had several limitations. First, the study included only subjects from a single institution, and the sample size was relatively small. Therefore, the sample might not have been representative. Second, the accuracy of evaluation of the subjective symptoms of dyspnea at rest or diagnosis of delirium might have been less than optimal, due to the retrospective nature of the study.

In conclusion, our findings revealed the existence of a close association between PPI and survival in patients with lung cancer receiving palliative

care. However, the index showed a low sensitivity for the prediction of less than three weeks' survival in patients with SCLC, probably due to the aggressive nature of this disease.

Figure legends

Figure 1 Kaplan-Meier curve for lung cancer patients, including both SCLC and NSCLC patients, divided according to the PPI at the cutoff level of 6.

Figure 2 Kaplan-Meier curve for patients with SCLC and NSCLC divided according to the PPI at the cutoff level of 6.

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