Impact of pre-treatment symptoms on survival after palliative radiotherapy

An improved model to predict prognosis?

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Abstract

Purpose

The purpose of this study is to find out if there is any correlation between symptoms and prognosis in patients who are undergoing palliative radiation therapy (PRT). And with these findings develop a better prognostic model to predict survival.

Method

A retrospective review of 102 PRT records was performed. The patients were treated between 2012 and 2015 and scored their symptoms before PRT on the Edmonton Symptom Assessment System (ESAS). Uni- and multivariate analyses were performed to identify potential predictive factors, and from these a predictive model was developed.

Results

Median survival was 246 days. Multivariate analyses confirmed the significance of 6 factors, from which a predictive model was developed. These were ESAS pain (while not moving), ESAS appetite, ECOG performance status, pleural effusion/ pleural metastases, iv. antibiotics during or within 2 weeks before PRT and no systemic cancer treatment. Median survival in patients with 5-6 of these predictive factors was 56 days, while patients with one or less had a median survival of 696 days.

Conclusion

Developing exact predictive models in cancer patients were PRT is considered is a difficult task to achieve, and many factors must be taken into consideration. Our model does however show great potential. Given validation in another population, it can serve as an objective tool for clinicians when recommending optimal treatment for patients.

Introduction

With Carsten Nieder as my mentor, we decided to study if we can create an improved prognostic model, with the use of ESAS scale and other potential prognostic factors, in patients where palliative radiotherapy is considered. This is in many ways a continuations of Kent Angelo's work in his 5th year study[1]. ESAS scale (Edmonton Symptom Assessment System) is a list containing several different symptoms were the patient has to number each symptom with a score of 0-10. Zero equaling no problem at all, and ten equaling worst possible discomfort. The scale contained eleven symptoms: Pain (not moving), pain (while moving), fatigue, nausea, dyspnea, dry mouth, appetite, anxiety/restlessness, sadness/depression, constipation and sleep. It also included an overall score.

Many patients have cancer which is so severe or advanced that it no longer can be treated by curative means. These patients often need radiation therapy (RT) to relieve symptoms, extend their life expectancy and have an overall better quality of life. However, studies have shown that aggressive treatment at the end of the life is an indicator for poor quality of care[2-4]. The reasons for this are many. From the patient's point of view this time would be better spent with family and loved ones. From the clinician´s point of view it is desirable to tailor the treatment after the patient's needs[5]. Taking into account that it can require weeks after initiation of RT to reach optimal symptom relief[6]. One could argue that treatment without much benefit can be seen upon as unnecessary use of resources, better spent providing other palliative care.

Thankfully, different fractionation regimes do exist. Varying in how resource consuming it is for the patient and the hospital. Small doses repeated over many fractions causes less toxicity, but are more cost and time consuming. A study conducted in Germany among patients who died within 30 days of starting RT, showed that half of the patients spent more than 60% of their remaining lifetime in RT. Only 58% completed the treatment. To ensure better quality of life in patients with a small remaining lifespan, they recommend more usage of single fractionation RT, as it is easier for the patient to complete and costs less[7]. It is however worth mentioning that some studies show tendencies to underutilization of RT[8].

According to Nieder et al., every patient should receive optimal treatment, with correct dosing and fractionation, where such treatment improves either daily life or functions. If that is not the case, we should focus less on aggressive treatment and avoid hospitalization when possible[9].

To achieve this, we would need objective models for predicting remaining time of life in cancer patients. Some models already exist, but unfortunately they often provide overoptimistic estimates,

leading to overtreatment[10, 11]. Nieder et al. previously developed one such predictive tool. This prediction model was based on the following factors i) Patients with lung or bladder cancer of any histological type; ii) those with an ECOG score of 3 or 4; iii) those presenting progressive disease outside the target volume(s) of radiotherapy; iv) those exhibiting levels of hemoglobin below the institutional limit of normal; v) those who received opioid analgesics at the start of radiotherapy; and vi) those who received steroids at the start of radiotherapy. It seemed to be fairly accurate and appeared clinically applicable due to its low risk of withholding RT, but is however only applicable to patients with primary lung or bladder cancer[9].

With this study we plan to evaluate if the use of ESAS scale combined with other potentially prognostic factors can result in a model which gives a more exact estimate of remaining life, in patients undergoing RT.

Method

I retrospectively reviewed 102 records of patients receiving palliative radiation therapy at the radiation ward in Nordlandssykehuset in Bodø from 2012 to 2015. All information regarding the patients was collected from DIPS (the hospitals electronic health record), including their medical records, treatment details, ESAS scale and time of death. Patients were chosen at random. We did however encounter a technical problem with documents containing ESAS scale went missing from DIPS after installation of a new version. In this period of time I therefore had to review patient's paper records.

Potential predictive factors that were included were many: Sex, age, days of survival after first fraction of RT, ESAS sale, ECOG score, hematologic markers, comorbidity, dose and fractionation, primary site of cancer, number of target volumes, the presence and site of metastases, smoking, use of steroids and use of opioids/ pump. Days of survival was censored from first fraction of RT. Patients who were still alive at data cut-off were censored from their last documented contact with the hospital. Patients who received consecutive treatments were censored after their first fraction of the new course. The ESAS scores included in the study were collected shortly before each course of RT. Only patients who had registered ESAS scores before RT were included in the study.

We used IBM SPSS version 22 to conduct the statistical analyses. We started with analyzing every variable that could potentially be a predictive factor for survival by itself using pearson chi-square and Fisher`s exact test. Variables that had a p-value < 0.1 (because of small study size) were included

in a multivariate analysis using logistic regression. The factors this test found to be the most important ones were used to create a score for predicting survival. Points were given depending on the factors p-values. One point was given to the factors with a p-value between 0.049 and 0.01 and two points to the factors with a p-value of <0.01, which had a bigger impact on survival.

We initially intended to use RT within 30 days as a co-primary endpoint, but given a population of only 102 patients, 11 of which received RT within the last 30 days of life, the statistical power was not sufficient. We therefore decided to use days of survival after first fraction of RT as the sole endpoint.

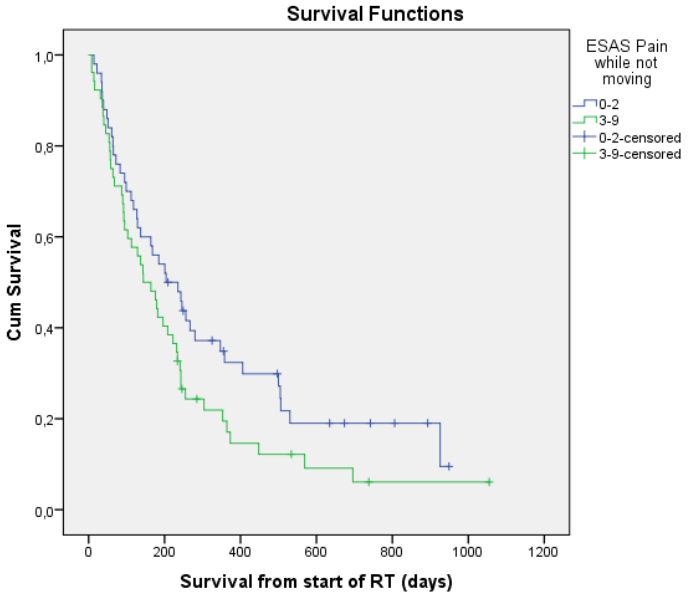
For the same reason, when analyzing the impact of ESAS scores we dichotomize the population by mean ESAS value, and compare the survival of patients with a score lower than median and higher than median.

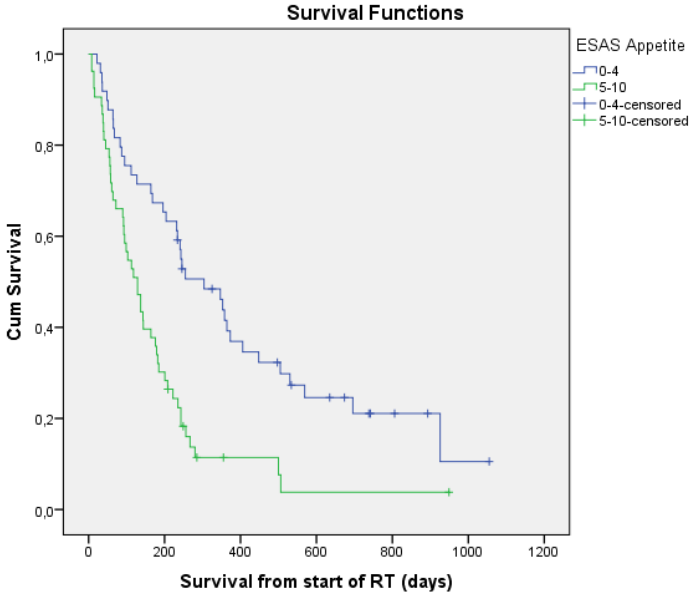
Results:

Of the 102 patients in this study 73.5% were males. The median age was 70 years (range 49-91). Median survival was 246 days. Median time from first cancer diagnosis to first fraction of RT was 32 months (range 0-236) and median time from first metastasis to first fraction of RT was 14.5 months (range 0-255). The most common types of cancer were prostate (30.4%), breast (11.8%) and lung cancer (non-small-cell) (25.5%). The one with the worst prognosis was by far lung cancer with an estimate survival of 95 days after the first fraction of RT, vs 241 and 347 respectively. The proportion that had progressive cancer outside of the RT region was about the same as the ones who didn't (47.1% vs 52.9%). They did however have a considerably worse prognosis with an estimate survival of 137 days after the first fraction of RT, vs 243 days (p-value <0.007). Only 74% of patients had measured their hemoglobin before RT, which was the highest represented hematologic marker. Given the small subgroups, we did not run any statistics on the importance of hematologic factors in predicting survival.

In univariate analyses we found 12 factors that by themselves were clear prognostic indicators for survival. These were ESAS dry mouth (p= 0), ESAS appetite (p = 0), ESAS constipation (p= 0.025), ESAS current state (p= 0.042), ECOG score of 3 or more (p = 0), time from first cancer diagnosis (p= 0.014), cancer type (p= 0.013), lung metastases (p= 0.015), bone metastases (p= 0.021), progressive disease outside of RT area (p= 0.007), pleural effusion/ pleural metastases (p= 0), iv. antibiotics within 2 weeks (p= 0.021), no systemic cancer treatment within 4 weeks before RT (p= 0). Although not

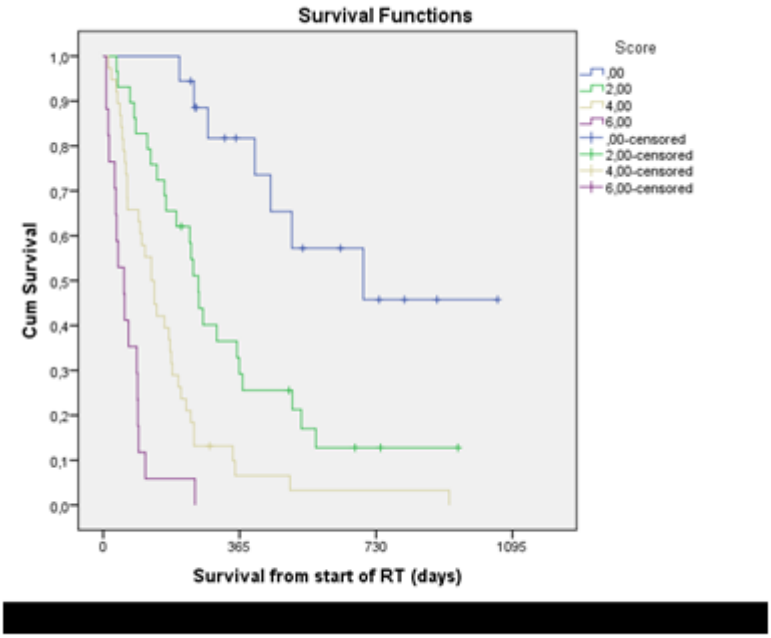
significant, we found six other factors that from their Kaplan-Meier survival graph showed clear trends of being a prognostic marker. In a bigger study, they might be significant. These were: ESAS pain (while not moving) (p= 0.08), ESAS shortness of breath (p= 0.084), more than one cancer diagnosis, (p= 0.07), adrenal gland metastases (p= 0.084) and the use of opioid pump (p= 0.079).





Multivariate analyses confirmed the significance of ESAS pain (while not moving), ESAS appetite, ECOG score, pleural effusion/ pleural metastases, iv. antibiotics during or within 2 weeks before RT and no systemic cancer treatment. The single most important factor was ECOG score (p= 0), followed by systemic cancer treatment (p= 0) and pleural effusion/ metastases (p= 0.006).

As seen from the graph below, our prognostic model based on these factors showed a clearly shorter survival in patients with a score point sum of two or higher. Those with a score point sum of 0-1 had an estimated median survival of 696 days, a score point sum of 2-3 an estimated median survival of 255 days, a score point sum of 4-5 an estimated median survival of 129 days and a score point sum of 6 or more an estimated median survival of 56 days (p= 0).



Calculation of the prognostic score

ECOG 2-4	2 points
Not receiving systemic treatment	2 points
Pleural effusion/ metastases	2 points
On iv antibiotics during last 2 weeks	1 point
ESAS appetite above 4	1 point
ESAS pain while not moving above 2	1 point

Discussion:

Being able to predict the remaining lifespan of terminally ill cancer patients will reduce over/under treatment, which in turn will lower costs and help clinicians provide treatment best suitable to their patients' demands. Developing better prognostic models can help us achieve this, by providing clinicians with objective tools. As Nieder et al. pointed out, short-course regimes with no or low-grade side effects exist, which improve symptoms such as pain, dyspnea and hemoptysis. Therefore, prediction tools must not predict short survival times in patients who survive long enough to experience a burden of symptoms, and must also identify the majority of patients who will succumb to disease too early to benefit from treatment[9].

There are some disadvantages to this study, mainly the fact that it is a retrospective study. Some variables were quite challenging to uncover, because of missing journal entries. This left us with small subgroups and difficulty to reach statistical significance. We initially intended to analyze the prognostic importance of blood tests before RT as other studies have found them to be significant[9], but this was not possible given the small population. Neither did we evaluate cause of death in the patients. Some of these patients may have died of other causes than their cancer. Something else worth noting was that not all people went through full restaging before their RT, and therefore the metastatic cancer may have been more advanced than expected.

Studies have previously shown the significance of a high ECOG score[9, 12] and the presence of pleural effusion in predicting RT during the last month of life[9]. Therefore, it is no surprise that these had prognostic value in our study as well. Chow et al. developed a prognosis model in 2002 which included primary cancer site, site of metastasis, Karnofsky performance status, ESAS fatigue, ESAS appetite and ESAS shortness of breath[12]. Their model was not all that different from ours, sharing two factors and all but "shortness of breath" were significant factors in our univariate analysis. They also did not include "use of systemic cancer treatment", "pleural effusion/metastases" nor "use of antibiotics" in their study.

Conclusion

Our predictive model showed a significantly reduced survival in patients who had a score of two or higher. Given that this study has a limited population and the fact that the model has not been validated in another population we recommend further research before implementing the model in everyday treatment. It is however clear that improved predictive models can be created, which may

give clinicians more objective tools to predict remaining lifetime. ESAS could be significant in one such model.

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