Baseline Quality of Life predicts Overall Survival in patients with mCRPC treated with 223Ra-dichloride

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Abstract

Rationale, aims and objectives. The prognostic value of baseline clinical parameters in predicting the survival prolonging effect of 223Ra-therapy in metastatic Castration Resistant Prostate Cancer patients is still an open issue. The aim of this study was investigating the impact of baseline Quality of Life on Overall Survival (OS) in mCRPC patients treated with 223Ra. The present study also evaluated the trend of patient-reported QoL during both 223Ra-treatment and post-therapy follow-up period.

Method 173 consecutive mCRPC patients treated with 223Ra were included in this prospective study. QoL was assessed through EORTC QLQ-C30 and QLQ-BM22 Questionnaires and 2264 questionnaires were evaluated. Other baseline variables relevant to the OS analysis have been considered. Data were summarized using descriptive statistics, univariate and multivariate analysis with Cox model. A principal component analysis (PCA) on the questionnaires' results compiled at baseline was performed to reduce the data to a one-dimensional score. Joint models for survival and longitudinal data were finally used in order to evaluate the relationship between the time-depended QoL scores and OS.

Results On multivariate analysis, baseline patients' Hb, tALP, and two EORTC QLQ-C30 items, physical functioning (HR=0.970,CI=0.960-0.980,p0.001) and dyspnea (HR=0.992,CI=0.986-0.999,p=0.023), were significantly associated with OS. In the resulting model of the multivariate analysis performed after PCA, baseline patients' Hb, tALP and QoL-score were independent significant predictors of OS (QoL-score:HR=0.995-95%CI=0.992 – 0.998,p=0.001). The OS analysis stratified by score of baseline QoL, showed a median OS of 8 (95%CI=6-11) and 16 (95%CI=12-24) months for scores respectively below and above the cut-off value (log-rank-p<0.001). The joint model showed a significant deterioration of QoL-score during both 223Ra-therapy and follow-up period (p<0.001).

Conclusion Baseline QoL is a significant predictor of OS, meaning that patients with better pretreatment QoL are more likely to obtain a marked survival prolonging effect from 223Ra.

Introduction

Bone metastases represent the end-stage of the disease for many patients with metastatic Castration Resistant Prostate Cancer (mCRPC)1. Such patients, dealing with disabling bone pain, hypercalcemia, spinal cord or nerve root compression, pathological fractures, and marrow failure, have poor prognosis and experience a significant worsening of their quality of life (QoL)2,3.

223Ra-dichloride (223Ra), a bone-targeting alpha-particle emitter with low bone-marrow toxicity4, was safety5 and approved for treatment of mCRPC patients with symptomatic bone metastases and no evidence of visceral metastatic involvement6, after the randomized phase III clinical trial (ALSYMPCA), showed palliative effect on bone pain and significant improvement of overall survival (OS) in treated patients7. Survival gain represents the distinctive feature of 223Ra-therapy, as compared to other palliative bone-targeting

therapies, such as local radiation, 89Sr and ^{153}Sm-EDTMP, Zoledronic acid and Denosumab, which have no impact on survival8. Although the role of 223Ra in improving OS is well established, with a reported median survival extension of 3.6 months as compared with placebo, few reliable and validated prognostic factors have been currently identified9. Several baseline variables commonly used in clinical practice10, such as Eastern Cooperative Oncology Group Performance Status (ECOG-PS), total Alkaline Phosphatase (tALP), hemoglobin (Hb) and number of prior systemic treatments, have been proposed. To date, tALP is considered to be the most reliable marker of response during 223Ra-treatment, but the prognostic value of pretreatment levels is still under investigation11,12. A recent study proposed a three variable prognostic score as a valid multidimensional approach for predicting the survival prolonging effect of 223Ra, by taking into account baseline patients' Hb, ECOG-PS and Prostate Specific Antigen (PSA)13. In such scenario, identifying further reliable prognostic factors, results of primary importance. Patient-reported QoL, intended as "patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal"14, has become an important consideration in clinical management of cancer patients and is known to be a significant prognostic factor for patients with different cancers, such as lung cancer15, colorectal cancer16, cholangio and hepatocellular carcinoma17, and head and neck cancer18. Nevertheless, little is known about the prognostic value of pretreatment baseline-QoL in patients with mCRPC prostate cancer undergoing palliative therapies, and no study has investigated the potential value of QoL-assessment in identifying subjects who are more suitable to receive the maximum survival benefit from 223Ra-therapy. The primary endpoint of this study was to evaluate the impact of pretreatment baseline QoL on OS, in mCRPC patients with symptomatic bone metastases receiving 223Ra-therapy. The present study also evaluated the trend of patient-reported QoL during both 223Ra-treatment and post-therapy follow-up.

Materials and Methods

This study was approved by the local Ethical Committee and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All patients signed a written Informed Consent. The present single-center prospective study enrolled 173 consecutive patients affected by symptomatic bone metastases from mCRPC, eligible for 223Ra-therapy7,19 and treated in our Nuclear Medicine Unit, from September 2013 to the time of the analysis (July 2018). Currently, 223Ra-therapy consists of an intravenous injection of 55 KBq/Kg of body weight, dispensed every 28 days, for a total of 6 cycles6. QoL was evaluated by asking patients to answer both the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30, version 3.0), and the EORTC Bone Metastasis Module (QLQ-BM22). The unavailability of the baseline QoL assessment represented an exclusion criterion from the study. The QLQ-C30 questionnaire represents a specific tool for the assessment of QoL in cancer patients20. The QLQ-C30 (version 3.0) is composed of both multi-item scales and single-item measures. These include 5 functional scales (cognitive, CF; emotional, EF; physical, PF; role, RF; and social functioning, SF), 3 symptom scales (fatigue, FA; nausea/vomiting, NV; and pain, PA), a global health status/QoL scale and 5 single items assessing additional symptoms (appetite loss, AP; constipation, CO; diarrhea, DI; dyspnea, DY; and sleep disturbance, SL) and perceived financial impact, FI. Each of the multi-item scales includes a different set of items—no item occurs in more than 1 scale. All scales and single-item measures range in score from 0–100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning. A high score for the global health status/QoL represents a high QoL. A high score for a symptom scale/item represents a high level of symptomatology/problems. The Bone Metastasis Module (QLQ-BM22) consists of an additional disease-specific module for patients with bone metastases21. The 22-item EORTC QLQ-BM22 questionnaire assesses disease symptoms related to bone metastasis, including painful sites, functional interference, painful characteristics, and psychosocial aspects as multi-item scales. We scaled all items from one (not at all) to four (very much). In this questionnaire, a higher score in the case of symptom scales is indicative of greater distress, while a higher score in the case of functional scales indicates greater functional ability. Questionnaires were completed by patients without any kind of conditioning from relatives or medical staff, and were submitted at baseline, at the end of each treatment cycle, and at each follow-up evaluation, performed at 3 months, 6 months and 12 months after the end of 223Ra-therapy. Among 173 patients enrolled, 5 were excluded from

the study because of the unavailability of the baseline QoL assessment. Other baseline clinical data relevant to the OS analysis, specifically age, height, weight, Hb, platelets (PLT), ECOG-PS, PSA and tALP, have been collected and taken into account in the statistical analysis. OS was established from the date of the first administration of 223Ra until the date of death from any cause.

Statistical Analysis

Continuous variables were expressed as mean +/- standard deviation; categorical variables as absolute and percentage values. OS was defined as the time span from first administration of 223Ra until death from any cause or censoring at last follow-up time. The Kaplan-Meier estimator was used to estimate survival curves. Univariate analysis using a Cox regression model were used to assess potential prognostic factors. A multivariable Cox regression model was then estimated where the final set of predictors was selected based on minimization of the Akaike Information Criterion in stepwise selection stages. The stepwise selection criterion protects from collinearity issues, which were also checked for the final selected model using Variance Inflaction Factors. No issues with collinearity were present in the models reported. We performed a principal component analysis (PCA) on the questionnaires' results compiled at baseline to reduce the data to a one-dimensional score. Data reduction was done considering the correlation matrix of the whole questionnaire with nineteen items (15 for the *EORTC QLQ-C30 and 4 for the EORTC QLQ-BM22).* PCA optimally assigns weights to each item, with each principal component (PC) resulting as a weighted linear combination of the original variables. The first PC has the largest possible variance and can be used as a univariate score summarizing the whole questionnaire. Data reduction was satisfactory as about 90% of total variance was captured by the first PC. Univariate and multivariate analyses using Cox models were then repeated to evaluate the role of the first principal component as a potential prognostic factor. Only baseline measurements were used for performing PCA in order to avoid attrition bias in estimating weights. Weights for the first PC were then used to build scores also at different follow-up times. In order to evaluate the relationship between the resulting time-dependent QoL scores and OS (and the relationship between trends and OS) we used Joint Models for survival and longitudinal data, where a single shared parameter captured the association of interest. Joint models allow to assess relationships with longitudinal markers and survival in an unbiased manner. The prognostic significance of the new scores was evaluated via time-dependent receiver operating characteristic (ROC) curves. The final cut-off was selected by maximizing the sum of sensitivity and specificity. A $p < 0.05$ was considered as statistically significant and all tests were two-sided. All statistical analyses were performed with the software R version 3.5.1.

Results

Baseline patients' characteristics are shown in Table 1. Among 168 patients, 108 patients (64%) had completed the 6 scheduled administrations, 48 patients (29%) had discontinued 223Ra because of progressive disease or death, while 12 (7%) were still receiving therapy at the time of the analysis. A total of 2264 questionnaires have been collected and analyzed, 1132 of which were EORTC QLQ-C30 and 1132 were QLQ-BM22. The median follow-up time from the first 223Ra-treatment to either death or last contact (last 223Ra administration, last follow-up phone call or last follow-up 99mTc-diphosphonate bone scan), was 11+-8 months (range 1-38). Median OS time was 12 months (95%CI 10 - 13 months), as shown in Figure 1. The univariate analysis evaluating the prognostic value of all baseline clinical variables showed that patients' Hb, PLT, tALP, and PSA values were independently associated with an increased risk of death. As shown in Table 2, almost all items of both baseline EORTC QLQ-C30 and QLQ-BM22 questionnaires were significantly associated with OS on univariate analysis. Only age (p=0.095), dyspnea (p=0.511), diarrhea (p=0.055) and financial difficulties (p=0.218) were not significantly associated with improvement in OS. When adjusting for other measures on multivariate analysis, baseline patients' Hb, tALP, and two EORTC QLQ-C30 items (PF2-physical functioning and DY-dyspnea) were significantly associated with OS. After data reduction, the first principal component (PC) explained 90% of the total variation, being then a satisfactory summary of the nineteen questionnaire items. The weights of the first PC are presented in Table 3. Each subject QoL score was calculated as the sum of the product of each loading and the corresponding item measurement. The score ranges from -222 to 200. The new QoL score showed good area under the

curve (AUC 0.73); ROC curve is shown in Figure 2. The threshold selected by maximizing the sensitivity and specificity was 7. The entire cohort was stratified into two subgroups on the basis of the baseline QoL cut-off so obtained; the estimated overall survival and log-rank test show that patients with a baseline QoL < 7 had a median OS time of 8 months (95%CI 6 - 11 months), while those with a baseline QoL [?] 7 had a median OS time of 16 months (95%CI 12 - 24 months), showing a significant association between higher levels of baseline QoL and longer survival (log-rank $p<0.001$) (Figure 3). The baseline value of our QoL score was significantly associated with OS at univariate analysis (HR = 0.993, 95% CI 0.991-0.996) with a p value <0.001 and when adjusting for other measures on multivariate analysis, baseline patients' Hb (HR = 0.816, 95% CI 0.717 – 0.927), tALP (HR = 1.008, 95% CI 1.003 – 1.013) and our QoL score (HR = 0.995, 95% CI 0.992 – 0.998) were significantly associated with OS (Table 4). The joint model showed a significant deterioration of global-QoL during both 223Ra-therapy, and the follow-up period ($p < 0.001$), as shown in Figure 4.

Discussion

The impact of the disease on patients' QoL, has become an important consideration in health care and a weighty factor in clinical management of cancer patients22. In recent years, the investigation whether baseline QoL-assessment, in addition to clinic-pathological factors, may improve prognostic stratification, has aroused a growing interest, and focused the attention on the development of reliable QoL-assessment questionnaires, designed to capture information directly from the respondent. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), is considered to be a valid self-completion questionnaire to reliably and accurately assess QoL in cancer patients and is to date one of the most widely adopted instruments in cancer research and clinical practice23. In several studies among patients with different cancer histologies, the EORTC QLQ-C30, often associated with disease-specific questionnaires, has proved to be a valid and reliable tool for the assessment of the correlation between QoL and OS. In a quality of life study among patients with gastro-esophageal cancer, the appetite-loss item of the EORTC QLQ-C30, resulted to be a significant independent predictor of survival, highlighting the significant prognostic role of QoL measures in this patient population24. A study involving patients with Platinum-resistant Ovarian Cancer (PROC) reported a median OS extension of 6.3 months and 6.0 months, in patients with better physical function score and lower abdominal/gastrointestinal symptom scores respectively25. The reported significant correlation of the abdominal/gastrointestinal domain of the ovarian specific questionnaire (OV28)26 with OS, confirmed the importance of using a disease-specific instrument in the assessment of QoL, in order to better evaluate QoL aspects more strictly correlated with each particular type of cancer, exceeding the limits of a general questionnaire for all cancer patients. Similar findings are reported in a recent study among patients with nasopharyngeal carcinoma treated with intensity modulated radiation therapy. In this study QoL was assessed by asking patients to answer the EORTC QLQ Head and Neck Cancer-Specific Module (H&N35)27 in addition to the EORTC QLQ-C30 (version 3.0). A high pretreatment cognitive functioning score in QLQ-C30 was associated with longer local recurrence-free survival, while H&N35 pretreatment teeth-ill and felt-ill were significantly correlated with progression-free survival and distant-free survival respectively28. For patients with bone metastases, particularly occurring in advanced breast, prostate, lung and renal cell cancers29, pain represents a heavy burden, often responsible for a significant worsening of QoL. The pain-centered questionnaire EORTC Bone Metastases Module (EORTC QLQ-BM22) was specifically designed as a supplement to the EORTC QLQ-C30 to evaluate the specific aspects of QoL impairment associated with bone metastases30. The present study is the first analysis of the prognostic value of baseline QoL measures in mCRPC patients with symptomatic bone metastases treated with 223Ra and was performed by submitting to patients both the EORTC QLQ-C30 and the EORTC QLQ-BM22. In accordance with the above studies among patients with different advanced cancers, baseline QoL showed a significant correlation with OS in our patient population. The resulting model of the multivariate analysis performed after PCA, showed that among patients with the same clinical condition in terms of baseline Hb and tALP values, those with better self-reported QoL, are more suitable to obtain a greater survival benefit from 223Ra. In particular, as shown in the OS analysis stratified by score of baseline QoL, the median OS is significantly longer in patients with higher baseline QoL scores as compared to

patients with lower scores, specifically 16 and 8 months of median OS respectively. A recent paper proposed a three-variable predictive score as a reliable and helpful tool for stratifying the expected OS of mCRPC patients treated with 223Ra, by taking into account the baseline arrangement of ECOG-PS, PSA and Hb13. Our analysis, underlining the significant correlation between baseline QoL and OS, suggest as including the baseline QoL assessment in a multi-variable model of baseline clinicopathological factors, may add prognostic potential, thus improving mCRPC patients' stratification about prognosis. Considering that the effect of 223Ra on OS is known to be obtained only after at least five cycles, stratifying patients' expected OS is of fundamental importance31. The EORTC QLQ-C30, represents a valid and complete instrument, provides significant results, as reported in previous systematic reviews and allows QoL assessment at a minimal cost32,33. In a previous paper, the QLQ-BM22 demonstrated to be a sensitive instrument for assessing palliative-radiotherapy benefits in patients with symptomatic bone metastases, by evaluating responders' QoL, before treatment and two months after treatment34. The pain domain of the QLQ-C30 and three out four domains of the QLQ-BM22, specifically painful sites, pain characteristics and functional interference, showed a significant improvement after treatment. This study confirmed the importance of using QLQ-BM22 as a bone metastases-specific tool when assessing QoL and evaluating response to palliative treatments in patients with symptomatic bone metastases. Our evaluation of QoL trend during 223Ra-therapy and follow-up period, performed through both the QLQ-C30 and the QLQ-BM22 questionnaire showed a global deterioration of QoL. These findings might be partially attributed to the inclusion of both responders and non-responders to 223Ra in terms of bone-pain relief, in the statistical analysis. Moreover, as we included all patients who had received at least one cycle of 223Ra, patients still in treatment were also evaluated, as well as patients with "flare phenomenon" in pain35,36, meaning that potential responders to treatment were included in the study before they obtained a significant benefit from all the 6 scheduled cycles of therapy. A patient-reported QoL analysis from the ALSYMPCA study, performed with the general EuroQoL 5D (EQ-5D) questionnaire37 and the disease-specific Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire38,39**,** demonstrated that in patients undergoing 223Ra-therapy, improved survival is associated with a slower decline in QoL over time as compared to placebo40. Despite our study showed similar results and confirmed QoL deterioration over time in mCRPC patients treated with 223Ra from baseline during both therapy and follow-up period, different instruments have been employed for QoL evaluation. These considerations might put the attention on the development of a standardized method to be applied in QoL assessment, in order to optimize the sharing of comparable data on patients' QoL outcomes between different centers, thus improving both research and clinical practice. A possible limitation of the present study is the analysis conducted only in a single center among a limited sample of patients.

Conclusion

The survival gain in patients with bone metastases from CRPC treated with 223Ra is well established, but the identification of baseline variables that may predict the individual response to treatment is a continuous challenge. In our analysis, the baseline QoL assessed through the EORTC QLQ-C30 and the EORTC QLQ-BM22, showed a significant correlation with OS, meaning that patients with better baseline QoL are more likely to obtain a marked survival prolonging effect from 223Ra-therapy. These findings suggest that patient-reported QoL measures, in addition to clinic-pathological factors, may improve prognostic stratification in mCRPC patients undergoing 223Ra-therapy, thus influencing clinical decision-making process and patient-doctor communication about prognosis.

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VF, MSDF, ADR. MP, AP, AF, LC, JL, GDV declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

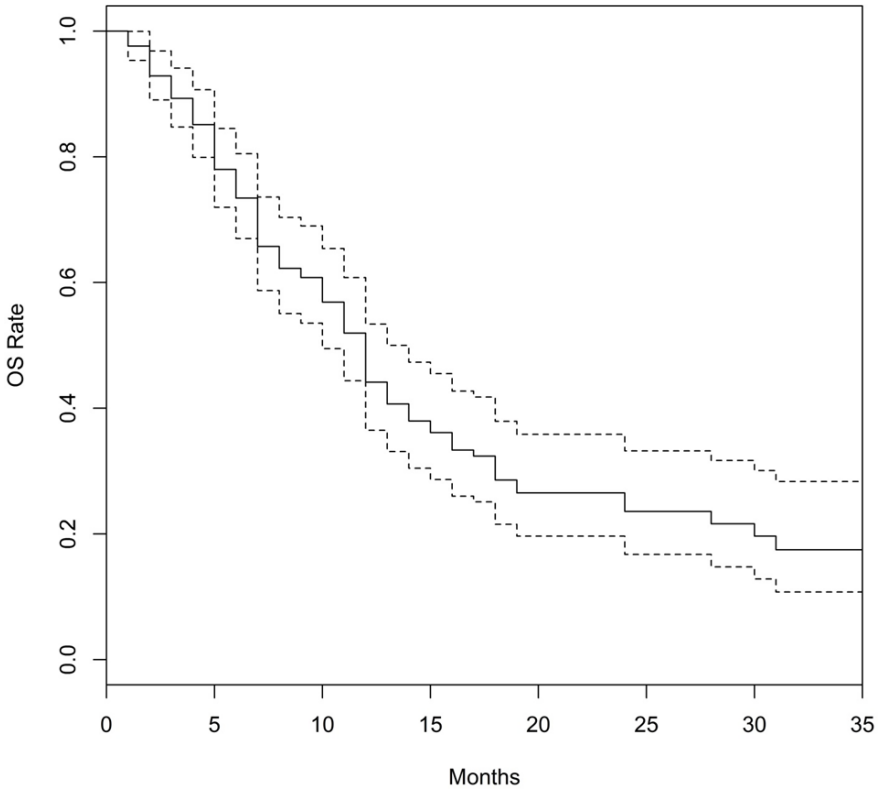
Figure Legend

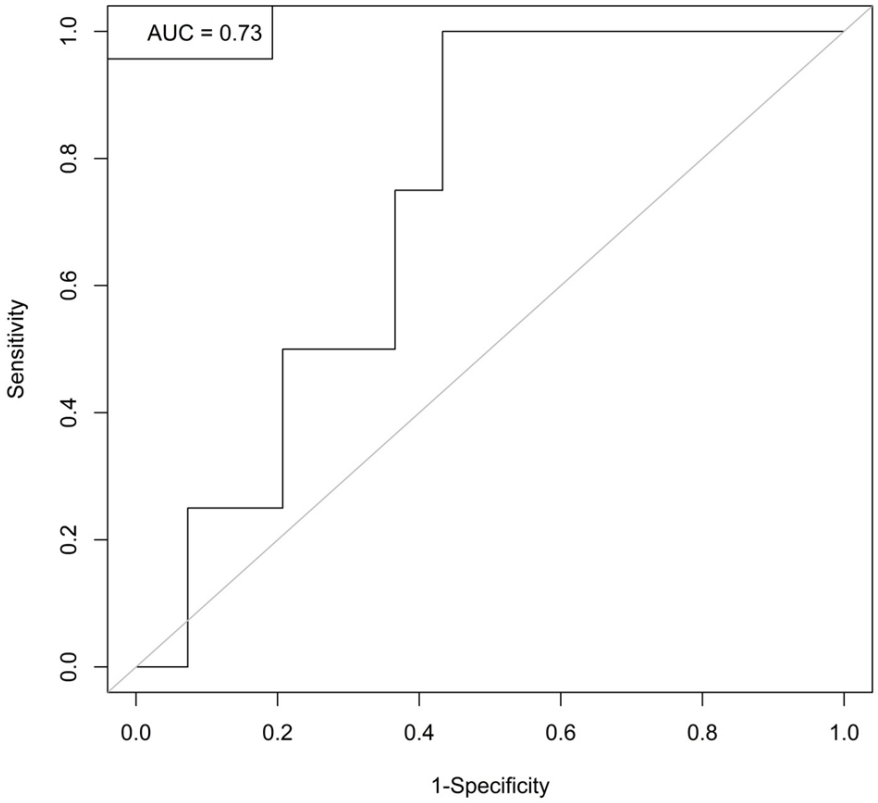
Fig. 1 Kaplan-Meier estimate showing overall survival in our cohort, with a 95% confidence interval in dashed lines

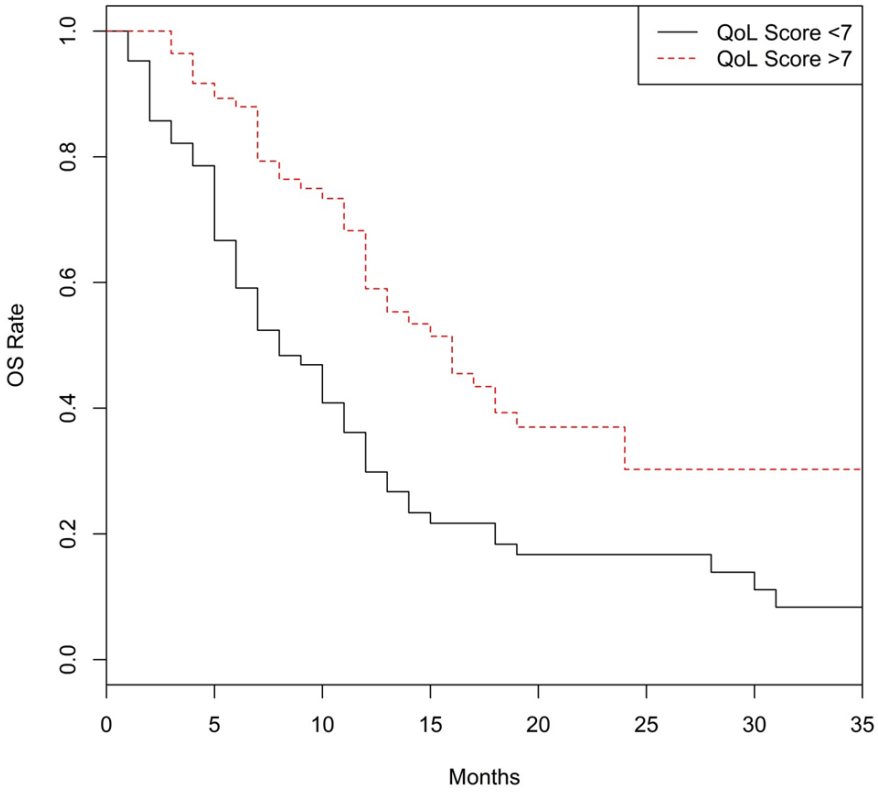
Fig. 2 ROC curve for baseline QoL Score

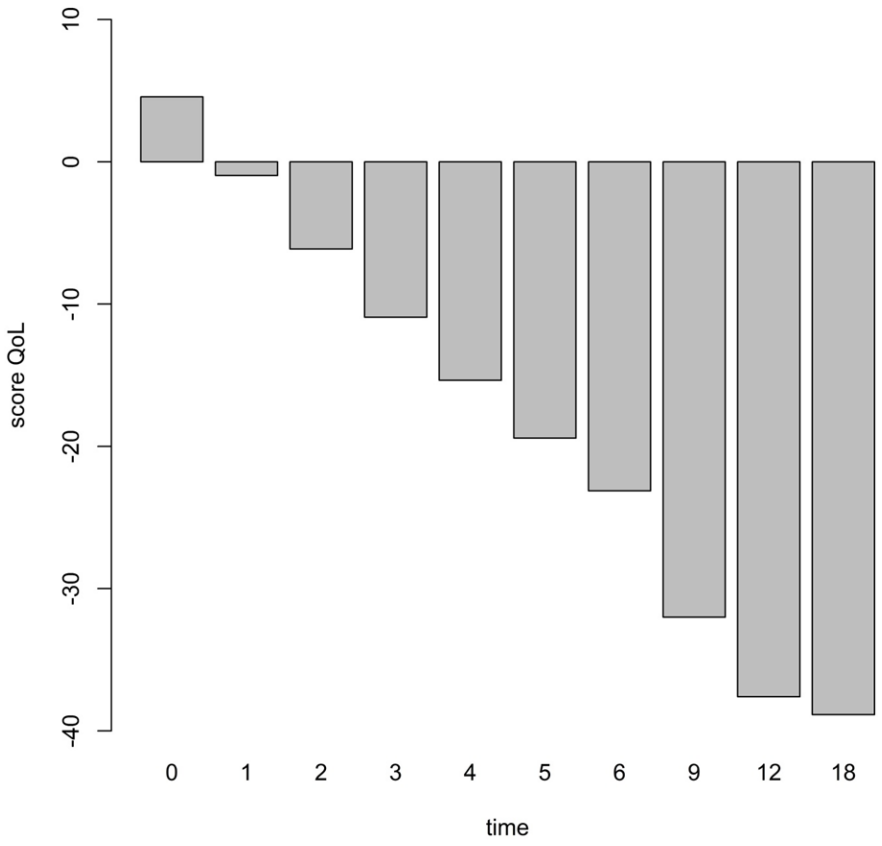
Fig. 3 Kaplan-Meier estimate showing overall survival stratified by QoL cut-off

Fig. 4 Deterioration of global-QoL score during both 223Ra-therapy, and the follow-up period









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