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Original article

Effect of age on response to palliative radiotherapy and quality of life in patients with painful bone metastases

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ABSTRACT

Background: Multimorbidity and declining performance in elderly cancer patients may result in less treatment benefit. We investigated whether age is a predictor for pain response and quality of life (QoL) after radiotherapy in patients with painful bone metastases.
Methods: The database of the Dutch Bone Metastasis Study was used (1996–1999). 1157 patients, irradiated for painful bone metastases, rated their pain, QoL-domains and overall health at baseline and during follow-up. Response was calculated taking into account changes in pain score and medication. Patients were grouped into three age cohorts: A: <65 ($n = 520$), B: 65–74 ($n = 410$) and C: ⩾75 years ($n = 227$).
Results: No significant difference existed in pain response between cohorts: 78% in cohort A, 74% in B and 67% in C. When assessing baseline QoL, a significant difference in activity level was noticed, with more impairment in elderly compared to younger patients (C versus B ($p = 0.01$), C versus A ($p < 0.001$)). Other QoL-domains were similar at baseline and during follow-up among cohorts. A pain response was significantly associated with improvement of health-related QoL (OR 3.74, 95% CI 2.66–5.25).
Conclusion: The majority of elderly patients with painful bone metastases responded to radiotherapy and showed comparable overall QoL compared to their younger counterparts. Age is not a predictor for pain response or QoL.
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The incidence of cancer increases with age [1–3]. Data from the last decades show that for the most common cancers, the percentage of patients aged 65 years and older is over 50% [2]. The number of elderly cancer patients is increasing due to a longer life expectancy, improved cancer treatments and increased tumor-specific survival [2,3]. Moreover, the aging of the babyboom era is coming. The number and proportion of elderly patients with cancer are thus expected to increase dramatically [3], with up to 42% of cancer patients in the United States in 2050 being 75 years and older [2]. Elderly patients with cancer represent a different and more fragile population than younger patients, with specific age-related problems and needs, related to multimorbidity and poorer physical or cognitive condition. They are frequently excluded from or underrepresented in clinical trials [4]. Therefore, trial outcomes and subsequent choices for medical treatments may not be applicable to this group. Studies show that elderly cancer patients receive different treatments than younger patients [5–8]. In both Canada and the United States, for example, elderly patients were less likely to be referred even for an effective palliative treatment such as radiotherapy [9–11].

Painful bone metastases have a major impact on quality of life (QoL) of cancer patients [12,13]. Radiotherapy with a single fraction of 8 Gray (Gy) is considered the standard treatment for patients with painful bone metastases, with a pain response rate of more than 60% [14–17]. The Dutch Bone Metastasis Study (DBMS) is the largest trial contributing to these outcomes, with 1157 patients included [14,17]. Both single and multiple fraction schedules were equally effective in treating pain, with a pain response in 73–75% of patients and no specific patient subgroups benefitting from higher total doses [14,17–20].

To determine whether palliative radiotherapy is justified in elderly patients with painful bone metastases, the DBMS database was used. We investigated whether age is a predictor for pain response and QoL after radiotherapy for painful bone metastases.

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Patients and methods

The DBMS was a nationwide, randomized controlled trial in patients with painful bone metastases. From 1996 to 1998, 1157 patients with painful bone metastases were randomized between a single fraction of 8 Gy or six fractions of 4 Gy. The main endpoint of the study was pain response. Detailed descriptions of the study protocol have been published previously [14,17]. The Medical Ethics Committees of all participating institutions approved the study. All patients provided informed consent.

Questionnaire

At randomization and during follow-up, patients filled out weekly questionnaires for twelve weeks and thereafter monthly until two years of follow-up, death or closure of the study in December 1998. These questionnaires contained a pain scale, QoL-related questions from the Rotterdam Symptom Checklist (RSCL) [21], a visual analogue general health scale (VAS health) and medication intake.

Analyses

For the present analyses, we used the pain scale, QoL scores of the RSCL and VAS health for twelve weeks after randomization. This time frame was chosen to limit the influence from tumor progression or other treatments. To study the effect of age, patients were grouped into three age cohorts: A: patients under 65 years, B: 65–74 years and C: 75 years and older.

Pain response analyses

Pain was measured on an 11-point numeric rating scale, from 0 (no pain) to 10 (worst pain imaginable). Following international criteria [22], pain response was defined as a decrease in the initial pain score by at least two points, without analgesic increase, or analgesic decrease without an increase in pain score. No fixed time interval from the date of randomization was applied. A response was calculated if at least two successive follow-up pain scores were available. Response analysis was possible in 1099 patients, because 58 patients (5%) did not return enough questionnaires to determine response.

Quality of life analyses

The RSCL consists of three QoL-subscales (psychological distress, physical symptom distress and activity level impairment, on a four-point Likert-type scale) and a scale for overall validation of life (on a seven-point Likert-type scale) [21]. Sum scores were calculated in accordance with the manual of the RSCL [21]. We reversed the scores of activity level impairment, with a high score indicating a high level of impairment. All QoL-scores were standardized to the range of 0–100, with 0 representing the best possible and 100 representing the worst possible condition. The VAS health was noted by patients on a line from 0 to 100, with 100 representing a poor general health situation. At baseline, the RSCL-domains, overall validation of life and VAS health were available in 94%, 94% and 92% of patients, respectively.

To assess the effect of palliative radiotherapy on health-related QoL, we compared the VAS health 8 weeks after treatment with the VAS health at baseline. If this score was missing at 8 weeks, we used the previous score at week 7 or 6. This time period was chosen because by then most responders had already noticed the effect of treatment, while possible transient side-effects had passed. Any decrease in VAS health, compared to baseline, was considered an improvement of QoL. If patients did not return their questionnaire or died within 8 weeks after treatment, this was considered a deterioration of QoL.

Statistical analysis

The database was analyzed using IBM SPSS statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) and SAS software (version 9.2, SAS Institute Inc., Cary, NC, USA).

For the categorical variables at baseline, Chi-Square tests were used. For continuous variables we used the one-way ANOVA, with Bonferroni post-hoc testing. Correlation between variables was studied using Pearson's correlation coefficients. To assess survival, we used Kaplan Meier method with a log-rank test. p-Values are based on 2-sided tests and considered significant if $p < 0.05$. To identify which variables predicted pain response and in particular to determine whether age is a predictor, Cox proportional hazard models were used. The preselected baseline variables, based on literature and clinical knowledge, were age (cohorts A/B/C), gender (male/female), Karnofsky performance score (KPS) [23] (90–100/70–80/$\leqslant$60), pain score (2–4/5–7/8–10), primary tumor (breast/prostate/lung cancer/other types), presence of visceral metastases (yes/no) and concomitant systemic therapy (yes/no). The full model contained all preselected variables. Subsequently, we eliminated the variables by backward selection with a threshold p-value of 0.20, until the model fit decreased significantly. The chosen p-value of 0.20 intends to limit the loss of information and to select also weaker predictors, although at the cost of including 'noise' variables [24].

For comparing the course of the QoL-domains over time between age cohorts, we used generalized estimating equations (GEE-measurements), a longitudinal data analysis technique. In all models, the outcome variables (RSCL-subscales and VAS health) were analyzed as a dependent variable using age cohort as a key independent variable. To identify predictors of improvement of health-related QoL (dichotomized into yes or no) and to determine whether age is a predictor, logistic regression was used. All preselected variables (at baseline: age, primary tumor, pain score, visceral metastases, gender, KPS and systemic therapy and during follow-up: pain response (yes/no)) were analyzed with a backward selection process with a threshold p-value of 0.20.

Results

Patient characteristics

Table 1 shows patient characteristics by age cohort. The mean age was 65 years (range 32–89 years). Cohort A (<65 years) consisted of 520 patients (45%), B (65–74 years) of 410 patients (35%) and C ($\geqslant$75 years) of 227 patients (20%). There were significant differences in gender and primary tumor between age cohorts. Patients older than 64 years were more likely to be male and to have prostate cancer, while patients in cohort A were more often females with breast cancer. At baseline, there were significant age differences in KPS ($p = 0.004$), the percentage of patients with KPS 20–60 being 26% in cohort A, 29% in cohort B and 39% in cohort C. Baseline pain scores were not significantly different between cohorts. Visceral metastases were more frequently present in patients younger than 65 years: 35% in cohort A compared to 24% in cohort B ($p < 0.001$) and 17% in cohort C ($p < 0.001$). Younger patients lived significantly longer than elderly patients: median survival was 35 weeks (cohort A), 27 weeks (B) and 27 weeks (C) respectively ($p = 0.047$).

Pain response

The overall pain response rate was 74%. Response was not significantly different between age cohorts: 78% in A versus 74%

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