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Polypharmacy in Older Patients ≥70 Years Receiving Palliative Radiotherapy

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Abstract. *Background/Aim: Many older cancer patients receive five or more daily medications (polypharmacy). The purpose of this study was to assess the prevalence of polypharmacy in older patients undergoing palliative radiotherapy and its influence on the risk of being unable to complete the prescribed number of fractions, as well as the 30-day mortality and overall survival. Patients and Methods: Retrospective review of 289 patients aged 70 years or older. Results: The median and mean Charlson comorbidity index (11) was 2, ranging between 0-7 (presently treated cancer not included). The median and mean number of daily medications was 7, ranging between 0-18. Only 27% of patients used less than 5 daily medications. Corticosteroids were used by 59% of the patients and opioid analgesics by 55%. Comorbidity, but also symptom severity, as indexed by pain medication, correlated significantly with the prevalence of polypharmacy. In multivariate analysis, neither polypharmacy nor use of corticosteroids or opioid analgesics influenced overall survival. No trends were seen for 30-day mortality or failure to complete radiotherapy. Conclusion: Polypharmacy is a common phenomenon in older patients receiving palliative radiotherapy and it does not predict adverse radiotherapy outcomes.*

Due to current trends in cancer incidence and demographics, an increasing number of older people are in need of oncological treatment (1). The favorable toxicity profile and high efficacy of radiotherapy make this treatment modality a preferred choice both in curative and palliative settings (2, 3). While older patients' eligibility for curative radiotherapy depends on comprehensive multidimensional assessment of biological age, organ function and other selection criteria, fewer restrictions are necessary when prescribing palliative regimens, especially short-course radiotherapy, which aims at symptom relief only (4). In daily practice, patients receiving palliative radiotherapy comprise a large group (5), with highly variable survival outcomes and different treatment aims (6, 7). Several screening tools have been developed to identify older patients with cancer who are likely to benefit from a complete geriatric assessment. Recently, an optimized tool was presented achieved high sensitivity, high specificity, better homogeneity across cancer types and greater parsimony with only six items needed (8). One of these items was polypharmacy, *i.e.* five or more medications daily. It has been suggested that greater attention to polypharmacy could lead to improvements in adverse drug events, cost, and possibly quality of life (9). The purpose of our study was to assess the incidence of polypharmacy in older patients undergoing palliative radiotherapy and its influence on the risk of being unable to complete the prescribed number of fractions, as well as the 30-day mortality and overall survival.

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Patients and Methods

Patients. A retrospective single institution analysis of 319 contemporary (2007-2014) consecutive in- and out-patients aged 70 years or older was performed. All were treated with palliative 2-D or 3-D radiotherapy (no stereotactic radiosurgery or stereotactic ablative body radiotherapy), *e.g.* for bone, lymph node or brain metastases, bleeding from their primary tumor or thoracic symptoms from lung cancer. Common fractionation regimens were 3 Gy ×10-13 or 4 Gy ×5-6. Their daily medications were recorded in the hospital's electronic patient records (EPR). As in other studies, polypharmacy was defined as five or more medications daily and extreme polypharmacy as ten or more (8-10). All drugs were taken into account, regardless of route of administration or indication. We excluded 30 out-patients because their medication records were older than 2 weeks when they started radiotherapy. Hematology and blood chemistry results immediately before radiotherapy were also available in the EPR (hemoglobin, leukocyte count, thrombocyte count, albumin, C-reactive protein, creatinine, lactate dehydrogenase, electrolytes).

Statistical analysis. Survival time was measured from the first day of palliative radiotherapy. We used IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA) for all evaluations. Actuarial survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. For multivariate analysis of survival Cox regression analysis was used (forward conditional method). All factors with significant *p*-value in univariate log-rank tests were carried forward to multivariate regression analysis. Associations between different variables of interest were assessed with the chi-square and Fisher exact probability test. Statistical significance was defined as $p<0.05$ throughout this study in two-sided tests.

Results

Demographics. The eligible cohort of 289 patients had a median age of 77 years and a range between 70-95 years (Table I). The median and mean Charlson comorbidity index (11) was 2 (range: 0-7; presently treated cancer not included). The median and mean number of daily medications was 7 (range: 0-18). Only 27% of the patients used less than 5 medications. Regarding the age strata displayed in Table I, the polypharmacy rate did not increase significantly with age. Corticosteroids were used by 59% of the patients and opioid analgesics by 55%, including 3% who received a continuous infusion *via* a pump.

Polypharmacy correlates with comorbidity and symptom severity. As shown in Table II comorbidity and symptom severity as indexed by pain medication, correlated in a statistically significant manner with the prevalence of polypharmacy. Comparable correlations existed for extreme polypharmacy. Very few patients with Charlson comorbidity index 3 or more used less than five daily medications and none of the patients required analgesia *via* an infusion pump.

Polypharmacy and survival. Median overall survival was 5 months (147 days). As shown in Figure 1, survival of patients with polypharmacy and extreme polypharmacy was worse (median: 231 and 152, respectively) compared to survival of patients with four or less medications (median: 96 days). However, the observed differences reached statistical significance only when comparing extreme polypharmacy to 0-4 medications.

Prognostic factors for survival. Patients who used corticosteroids had significantly shorter survival than non-users (median 117 *vs*. 170 days, $p=0.0001$, Kaplan-Meier curves not shown). The same was true for opioid analgesics (median 104 *vs*. 281 days, $p=0.0001$) and in particular pump administration (median 40 days). Significantly shorter survival was also found in patients with reduced performance status, brain metastases, liver metastases, lung metastases, adrenal gland metastases, higher Glasgow prognostic score (0: normal C-reactive protein and albumin, 1: abnormal C-reactive protein or albumin, 2: abnormal C-reactive protein and albumin) (12), higher Charlson comorbidity index and those not on systemic treatment. Patients without distant metastases survived significantly longer than patients with distant metastases (median 262 *vs*. 127 days, $p=0.01$). Patients with prostate, breast or kidney cancer survived significantly longer than those with other cancer types (median 308, 275, 176 days; others: 80-113 days, $p=0.02$). Factors such as gender, anemia, other hematology and blood chemistry results, active/previous smoking, and bone metastases were not associated with survival.

Table I. *Patient characteristics*.

Parameter	Number of patients	Percentage
Females	77	27%
Males	211	73%
Age 70-74 years	86	30%
Age 75-79 years	103	36%
Age ≥80 years	100	35%
No comorbidity	37	13%
Charlson comorbidity index 1	46	16%
Charlson comorbidity index 2	89	31%
Charlson comorbidity index ≥3	117	40%
No use of daily medication	3	1%
1-4 daily medications	76	26%
5-9 daily medications	125	43%
≥10 daily medications	85	29%
Performance status ECOG 0	17	6%
Performance status ECOG 1	71	25%
Performance status ECOG 2	101	35%
Performance status ECOG 3	85	29%
Performance status ECOG 4	15	5%
Prostate cancer	115	40%
Breast cancer	15	5%
Lung cancer (small/non-small cell)	16/65	6/22%
Bladder cancer	26	9%
Colorectal cancer	19	7%
Other cancers	33	11%
No distant metastases	46	16%
Distant metastases	243	84%
On systemic treatment	77	27%
Glasgow prognostic score 0	94	33%
Glasgow prognostic score 1	132	46%
Glasgow prognostic score 2	63	22%

ECOG, Eastern Cooperative Oncology Group.

In multivariate analysis, neither polypharmacy nor use of corticosteroids or opioid analgesics influenced overall survival (data not shown). Significant prognostic factors were performance status ($p=0.0001$), favorable cancer type (prostate, breast, kidney; $p=0.0001$), absence of distant metastases ($p=0.0001$), absence of liver metastases ($p=0.01$) and Glasgow prognostic score ($p=0.008$).

Polypharmacy and other endpoints. The number of daily medications was neither significantly associated with 30-day mortality nor failure to complete radiotherapy. No trends were seen either (data not shown).

Discussion

Multiple and/or inappropriate use of medications in seniors is a significant public health problem and cancer treatment escalates its prevalence and complexity. Although no single polypharmacy cut-point is optimal for predicting multiple adverse events in older people with cancer, the common definition of five or more medications is reasonable for identifying 'at-risk' patients for medication review (13). A study of 234 senior adults with cancer found a mean number of medications of 9 (10). The prevalence of polypharmacy, excessive polypharmacy and potentially inappropriate medication use was 41%, 43% and 51%, respectively. A different study included 2282 patients (advanced cancer pain patients, defined by a need for a World Health Organization analgesic ladder step III opioid) from 17 Centers in 11 European countries (14). They received a mean of 8 drugs. Over one-quarter used 10 or more medications. The drug classes most frequently co-administered with opioids were proton pump inhibitors, laxatives, corticosteroids, paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs, metoclopramide, benzodiazepines, anticoagulants, antibiotics, anticonvulsants, diuretics and antidepressants. Approximately 45% of patients received unnecessary or potentially unnecessary drugs, and about 7% were given duplicate or antagonizing agents. In an Australian study, polypharmacy was also highly prevalent (57%) in older people (≥70 years) with cancer and associated with impaired physical function and being pre-frail and frail compared to being robust (15) and associated with higher Charlson comorbidity index scores. In one study with 117 patients aged ≥65 years with newly-diagnosed cancer treated at ambulatory oncology clinics at an academic medical center, the prevalence of polypharmacy (≥5 medications) was as high as 80% (16). An increase in comorbidity count by one and ECOG performance status by one was associated with an increase in medication use by 0.48 (p=0.0002) and 0.79 (p=0.01), respectively. This issue might be aggravated by additional use of non-reported complementary or alternative medications (17).

These high prevalence figures prompted us to perform a similar study in patients aged 70 years or older who were treated with palliative radiotherapy, either in an ambulatory or in-patient setting. Comparable to previous studies we did not limit our analysis to one type of cancer. Although most patients with incurable cancer receive comparable supportive and anticancer drugs (analgesics, anti-emetics, chemotherapy, bisphosphonates *etc.*), a primary cancer-specific study limited, *e.g.*, to prostate cancer may facilitate a better correlation analysis. The median and mean number of daily medications in our study was seven. Only 27% of patients used less than five medications. Charlson comorbidity index and symptom severity, as indexed by pain medication, correlated with the prevalence of polypharmacy. In multivariate analysis, neither polypharmacy nor use of corticosteroids or opioid analgesics influenced overall survival. Polypharmacy was neither significantly associated with 30-day mortality nor failure to complete radiotherapy. No trends were seen either. These findings are in line with those from other recent oncology studies, which are summarized in Table III. However, some of these studies suggested correlations between polypharmacy and chemotherapy toxicity. Since palliative radiotherapy results in very low rates of serious toxicity, this end-point was not evaluated in our study. Future research should focus on radical radio(chemo)therapy, which has a different side-effect profile. Ideally, quality of life and adverse events would be recorded prospectively.

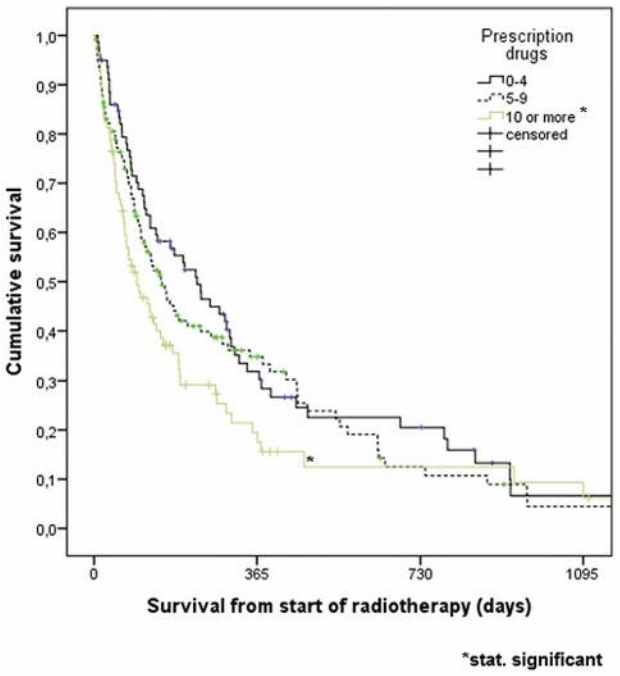

Figure 1. *Overall survival (Kaplan-Meier estimates) for patients with 0-4 daily medications (median: 231 days), 5-9 daily medications (median: 152 days) and 10 or more daily medications (median: 96 days), p=0.38 (0-4 vs. 5-9), p=0.02 (0-4 vs. ≥10), p=0.09 (5-9 vs. ≥10).*

Even if polypharmacy did not predict adverse radiotherapy outcomes in terms of short survival or failure to complete the prescribed number of fractions, its prevalence was so high that clinical practitioners should be educated about optimal medication use and avoidance of inappropriate medications in order to spare patients unnecessary toxicity and costs. In an Irish study, one week before death one-third of patients continued to be prescribed aspirin, and over one-quarter a statin (22). On the other hand one has to acknowledge that immobilized patients with severe pain often require opioid analgesics combined with a non-opioid and/or co-analgesic, laxatives, anticoagulation and

Table II. *Association between polypharmacy and comorbidity/pain management. p-Values less than 0.05 indicate statistical significance and are highlighted in bold.*

Parameter	<5 medications	5-9 medications	≥10 medications	Significance level
Charlson comorbidity index 0	62%	35%	3%	
Charlson comorbidity index 1	28%	48%	24%	
Charlson comorbidity index 2	31%	39%	29%	
Charlson comorbidity index 3	10%	49%	43%	
Charlson comorbidity index >3	11%	43%	46%	***p*=0.0001**
No diabetes mellitus	29%	43%	28%	
Diabetes mellitus	14%	38%	48%	***p*=0.045**
No cardiac comorbidity	39%	39%	22%	
Cardiac comorbidity	13%	48%	39%	***p*=0.000002**
No COPD	31%	44%	26%	
COPD	14%	38%	48%	***p*=0.004**
No opioid analgesics	42%	41%	16%	
Opioid analgesics, no pump	16%	46%	38%	
Opioid analgesics, infusion pump	0%	20%	80%	***p*=0.0001**

COPD, chronic obstructive pulmonary disease.

Table III. *Recently published literature data.*

Reference	Setting, cohort	Results
Woopen *et al*. 2016 (18)	Individual participant data meta-analysis of data from three phase II/III studies of the North-Eastern German Society of Gynecological Oncology, chemotherapy for recurrent ovarian cancer (N=1213)	An increasing number of medications was associated with overall grade III/IV toxicity ($p<0.001$), and hematological ($p<0.001$) and non-hematological ($p<0.001$) toxicities. Unplanned discontinuation of chemotherapy was not influenced by medication. There was no association of polypharmacy with overall survival.
Park *et al*. 2016 (19)	229 elderly head and neck cancer patients who underwent definitive treatment	Polypharmacy was not significantly associated with treatment-related toxicity, but with modestly increased prolonged hospitalization ($p=0.08$) and non-cancer health events ($p=0.05$).
Maggiore *et al*. 2014 (20)	500 adults aged 65 and older with cancer undergoing chemotherapy	No association was found between number of daily medications and toxicity or hospitalization.
Hamaker *et al*. 2014 (21)	78 elderly (≥65 years) metastatic breast cancer patients treated with first-line palliative chemotherapy in a randomized trial	Polypharmacy was the only individual factor significantly associated with toxicity ($p=0.001$).

stomach ulcer prophylaxis. Therefore, use of five or more daily medications is not always inappropriate.

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