Symptom Burden in Patients with Oligometastases at the Start of Palliative Radiotherapy

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Abstract

Background/Aim: Recent studies suggested that patients with oligometastases have a better prognosis compared with those who have widespread dissemination. In both groups, radiotherapy is a commonly applied treatment. Patient-reported symptoms might depend on the burden of disease. Possibly, oligometastatic patients report lower scores for symptoms such as fatigue or reduced appetite, which tend to worsen as the disease progresses to a later stage. Therefore, we analyzed the symptom scores in two groups of patients with or without oligometastatic disease. Patients and Methods: A retrospective study was performed of 83 patients who received palliative, non-ablative radiotherapy for distant metastases. The Edmonton Symptom Assessment Scale (ESAS) was employed to assess the pre-radiotherapy symptoms. Results: The oligometastatic group was smaller than anticipated (n=11). The ESAS score differences were not statistically significant. However, oligometastatic patients reported less fatigue, pain and dry mouth (p<0.2). They also had a better performance status. The median survival of oligometastatic patients was longer (8.1 *vs.* 5.5 months, p=0.17), in the absence of ablative metastases-directed treatment. Conclusion: The oligometastatic state is not a major contributor to the variable patient-reported symptom scores.

The detection and management of oligometastatic tumors has improved during the last 5-10 years (1, 2). Considerable research efforts are undertaken to further improve the outcomes in this biologically distinct subgroup of patients (3-7). Radiotherapy with ablative doses has gained increasing acceptance in this setting, but palliative radiotherapy continues to represent an important treatment option. Typical indications include pain, dyspnea, and neurological complaints. Ideally, these symptoms should be quantified and recorded before treatment, and monitored afterwards. One of the established tools that have been implemented by cancer hospitals is the Edmonton Symptom Assessment System (ESAS) (8-12). This short, one-sheet questionnaire addresses major symptoms and wellbeing on a numeric scale of 0-10 (highest symptom severity 10), including pain, nausea, fatigue, depression and others. Symptoms that are related to advanced disease might be more prevalent in patients with widespread metastases compared with those who harbor oligometastases. In particular fatigue, appetite and overall wellbeing are expected to worsen as the burden of metastases increases. To test this hypothesis, we performed a retrospective study addressing the symptom severity in patients with oligometastatic cancer who started palliative radiotherapy at our Institution.

Patients and Methods

The study included 83 patients at an academic teaching hospital who received palliative radiotherapy for metastatic solid tumors during the time period 2013-2015, as already described (9, 11). None of the patients had received stereotactic radiotherapy. The ESAS tool was administered by a registered oncology nurse immediately before oncologist consultation and imaging for treatment planning, *i.e.* approximately 1 week before palliative radiotherapy. Oligometastases were defined

as a maximum of 5 distant metastases (not counting locoregional lymphatic metastases) at one site. Examples include 5 brain metastases, 5 liver metastases or 5 bone metastases. The number was derived from the most recent radiology report available before the start of radiotherapy. All medical records were available in the hospital's electronic patient record system. Baseline characteristics, treatment and date of death or last contact were abstracted. Statistical analysis was performed with IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA). We employed the chi-square test (when appropriate, Fisher exact probability test or *t*-test). A *p*-value of 0.05 or less was considered statistically significant. Two-tailed tests were performed. Actuarial survival from the start of radiotherapy was analyzed with the Kaplan–Meier method and the log-rank test. Ethical approval was not required for this secondary analysis of the database, in accordance with national and institutional guidelines.

Results

The baseline characteristics of the study population are shown in Table I. The mean age was 70 years, standard deviation 9 years. Eleven patients had oligometastatic disease (13%). The location was in the bones (n=4), brain (n=5) and lungs (n=2). As shown in Table II, the median ESAS scores were not significantly different between the two groups. However, oligometastatic patients reported less fatigue, pain and dry mouth ($p<0.2$). In addition, the rates of moderate to severe symptoms (ESAS score at least 4) were evaluated in oligometastatic patients. A dyspnea score of at least 4 was reported by 6 of 11 patients. The rate was identical for poor sleep. The respective numbers were 5 of 11 for overall wellbeing, appetite and fatigue. Lower rates of moderate to severe symptoms were reported for all other ESAS items.

Oligometastatic patients had better performance status (0-1 in 64% compared with 33% in non-oligometastatic patients, *p*=0.09). Median overall survival was 8.1 months for patients with oligometastases and 5.5 months for those with a larger number of metastases (*p*=0.17).

Discussion

Patients with oligometastases commonly receive intense local, metastases-directed treatment, e.g. surgical resection, stereotactic radiotherapy and combined modality approaches (3, 4, 7, 13, 14). Selected patients continue to receive traditional palliative treatments, because their prognosis is less favorable, e.g. due to old age or considerable comorbidity and reduced organ function. We hypothesized that oligometastatic patients managed with palliative radiotherapy might report less symptom burden compared with patients who harbor widespread metastases. While maximum pain intensity from a single lesion might be comparable to that from more than one lesion, less site-specific symptoms such as fatigue and reduced appetite might better reflect the general burden of disease.

Inspired by other clinicians (10, 15, 16), we chose to adopt the ESAS scale as a pre-radiotherapy evaluation tool in daily routine and continue to perform this assessment today. Like previous retrospective studies, the present one is mainly hypothesis-generating and in addition hampered by the small number of patients and the fact that all patients were selected for palliative radiotherapy. Additional analyses in patients managed with stereotactic radiotherapy are also recommended. As shown in Table II, the ESAS scores were not significantly lower in patients with oligometastases. Possibly, the numerically lower scores for reduced appetite, fatigue, pain and dry

mouth may reach statistical significance in larger studies. It is therefore recommended to analyze additional cohorts of patients, e.g. from multicenter studies. Importantly, a small number of patients with oligometastases reported ESAS scores of up to 10 (maximum symptom severity) for pain, anxiety and constipation. This finding suggests that multidisciplinary palliative care may be needed in addition to radiotherapy to optimize symptom control and improve overall quality-of-life (11, 17, 18). Interestingly, oligometastatic patients had better performance status (0-1 in the majority, 64%) and this difference might in part explain the survival results observed in our study. It is not clear whether the small difference in median survival (8.1 months *vs.* 5.5 months) resulted from better performance status, oligometastatic disease itself or both. The outcomes reported after ablative treatment of oligometastases were much better than the present ones (2, 4, 7). Overall, the present study suggests that the oligometastatic state is not a major contributor to the variable patient-reported symptom scores, and that additional efforts are needed to better define the optimum management approach, also with regard to supportive care.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contribution

CN participated in the design of the study and performed the statistical analysis. TAK collected patient data. CN, and TAK conceived the study and drafted the article. All Authors read and approved the final article.

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Table I. Baseline characteristics before palliative radiotherapy in 83 patients.

Variable		N (%)
ECOG performance status	0	12 (15)
	1	19 (23)
	2	29 (35)
	3 or 4	23 (28)
Gender	Male	62 (75)
	Female	21 (25)
Primary tumor site	Prostate	30 (36)
	Breast	12 (15)
	Lung (small cell)	1 (1)
	Lung (non-small cell)	22 (27)
	Colorectal	5 (6)
	Bladder	1 (1)
	Malignant melanoma	3 (4)
	Kidney	4 (5)
	Other	5 (6)
RT target type[a]	Bone metastases	61 (73)
	Brain metastases	12 (14)
	Lymph node metastases	6 (7)
	Lung or thorax	8 (10)
	Prostate	3 (4)
	Other	3 (4)
Systemic cancer treatment	No	9 (11)
	Before RT	74 (89)
Time from first cancer diagnosis to RT, months	Median, range	34, 0-164
Time from first metastasis (if any) to RT, months	Median, range	15, 0-52

ECOG: Eastern Cooperative Oncology Group; RT: radiotherapy. [a]More than one possible in the same patient.

Table II. Edmonton Symptom Assessment Scale (ESAS) score before palliative radiotherapy in 83 patients. Data are the median score and range (minimum, maximum).

	Symptom											
Oligometastases	Dyspnea	Appetite	Dry mouth	Sad/depressed	Anxious	Pain (in activity)	Pain (at rest)	Constipation	Fatigue	Poor sleep	Nausea	Overall well-being
Yes	4, 0-6	1, 0-9	0, 0-5	2, 0-9	3, 0-10	2, 0-10	0, 0-7	0, 0-8	3, 0-7	4, 0-8	0, 0-5	4, 0-10
No	2, 0-10	5, 0-10	2, 0-9	2, 0-10	2, 0-10	5, 0-10	3, 0-9	2, 0-10	5, 0-10	2, 0-10	0, 0-8	4, 0-10
Significance level	0.7	0.5	0.12	0.9	0.3	0.18	0.11	0.5	0.19	0.08	0.8	0.4