

Symptom Burden in Patients Treated With Palliative Radiotherapy Before and During the COVID-19 Pandemic

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Abstract. *Background/Aim:* Oncological care has faced several challenges during the COVID-19 pandemic, e.g. treatment delay and worsening symptoms. Patient-reported anxiety, depression and sleep quality might have changed due to these special circumstances. Therefore, we analyzed the symptom burden of patients treated with palliative radiotherapy at our center. *Patients and Methods:* A retrospective study was performed of 50 consecutive patients and the results were compared to those obtained in a previous pre-COVID study. The Edmonton Symptom Assessment Scale was employed to assess the pre-radiotherapy symptoms. *Results:* The highest mean scores were reported for pain in activity (3.2) and dry mouth (3.1). Regarding anxiety, sadness/depression and sleep, the corresponding scores were 1.5, 1.2 and 2.7, respectively. Compared to the previous study, no significant increases were found. Most items had numerically lower mean values, e.g. anxiety (1.5 vs. 2.7). Both study populations had comparable median age (70.5 vs. 70 years), gender distribution and proportion of patients with bone metastases. However, there were two significant imbalances, namely a lower proportion of patients with prostate cancer (12 vs. 30%, $p=0.02$) and breast cancer (0 vs. 12%, $p=0.02$). *Conclusion:* In patients who showed up for radiation treatment planning, the suspected increase in anxiety, sadness/depression and sleep disturbance was not demonstrable. It is not known whether or not patients with substantial worries chose to decline referral to palliative radiotherapy. Therefore, comprehensive large-scale studies of patterns of care are needed to fully understand the impact of COVID-19-related measures.

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Despite major challenges and changes introduced by the rapid and global spread of COVID-19, palliative cancer therapy has continued to improve the overall situation, symptom burden and quality of life of many patients even in 2020. Recommendations were made regarding shortened and otherwise adapted treatment regimens, which also affected the practice of palliative radiotherapy (1-4). Uncertainty about treatment safety, management of side-effects and fear of infection with potentially fatal outcome has led to worried patients, often expressing many more concerns or delaying treatment than in the pre-COVID era (5-7). Anxiety, depression, loneliness and sleep disturbance are among the problems reported in different studies using different methods of symptom recording.

At the Department of Radiation Oncology at Nordland Hospital Trust, the Edmonton Symptom Assessment System (ESAS) has routinely been used for several years (8-10). This short, one-sheet questionnaire addresses major symptoms and well-being on a numeric scale of 0-10 (highest symptom severity 10), including pain, nausea, anxiety, depression, sleep and others. Due to the availability of pre-COVID ESAS data and concerns about high symptom burden experienced by patients treated after the start of the pandemic, we performed a retrospective comparison of the pre- and during-COVID pandemic symptom severity in patients who started palliative radiotherapy at our Institution.

Patients and Methods

In the pre-COVID study of 102 patients, a mean anxiety severity of 2.7 (standard deviation=3.2) was reported (8). Commonly, a threshold of 4 is regarded as important, because it indicates moderate to severe symptoms (11, 12). In order to detect a mean score increase to more than 4 in a new cohort of patients with 80% power and $\alpha=0.05$, 50 patients were needed (for mean score of 4.3 to report the precise calculation). Therefore, we decided to include 50 consecutive patients assessed with the ESAS. On March 10th, the Norwegian Institute of Public Health (www.fhi.no) had registered 277 people with confirmed SARS-COV-2 infection and different national measures were taken. Therefore, we included patients assessed after Saturday, March 14th in the present study.

Table I. Baseline characteristics before palliative radiotherapy in 50 patients.

Variable	N (%)
Gender	
Male	31 (62)
Female	19 (38)
Primary tumor site	
Prostate	6 (12)
Lung (small-cell)	5 (10)
Lung (non-small-cell)	15 (30)
Colorectal	6 (12)
Bladder	4 (8)
Malignant melanoma	3 (6)
Kidney	2 (4)
Multiple myeloma	5 (10)
Other	4 (8)
RT target type ^a	
Bone metastases	32 (54)
Brain metastases	10 (17)
Lymph node metastases	4 (7)
Lung or thorax	8 (14)
Prostate	1 (2)
Other	4 (7)
Systemic cancer treatment	
No	16 (32)
Planned after RT	4 (7)
During and/or after RT	30 (60)
RT indication	
Symptom palliation	39 (78)
Prevention or imaging findings	11 (22)
RT fractionation	
<5	6 (12)
5-9	18 (36)
10	18 (36)
>10	8 (16)

RT: Radiotherapy. ^aMore than one possible for the same patient.

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 (typical regimens: 8 Gy × 1, 4 Gy × 5, 3 Gy × 10). 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. Actuarial survival from the start of radiotherapy was analyzed with the Kaplan–Meier method.

Results

The baseline characteristics of the study population are shown in Table I. Many patients had lung cancer. The median Karnofsky performance status was 80 (range=50–100). The median age was 70.5 years (range=48–93). Fifteen patients (30%) were treated at the time of their cancer diagnosis and the others after intervals of 2–224 months (median=14 months). At the time of the analysis, 15 patients (30%) had died and the others had a median follow-up of 3 months. The actuarial median survival had not yet been reached and the 6-month survival rate was 60%.

Table II. Edmonton Symptom Assessment Scale score before palliative radiotherapy in 50 patients. Data are the mean score±standard deviation and range (minimum-maximum).

Symptom	Study	
	Present	Previous (8)
Dyspnea	1.9±2.6 (0–10)	2.6±2.8 (0–10)
Appetite	2.1±2.8 (0–10)	3.8±3.3 (0–10)
Dry mouth	3.1±3.0 (0–9)	2.9±2.8 (0–10)
Sad/depressed	1.2±1.8 (0–6)	2.1±2.8 (0–10)
Anxious	1.5±2.3 (0–8)	2.7±3.0 (0–10)
Pain (in activity)	3.2, 2.6, 0–10	4.4±3.2 (0–10)
Pain (at rest)	2.4±2.6 (0–10)	2.8±2.6 (0–9)
Constipation	1.2±2.5 (0–10)	2.5±3.1 (0–10)
Fatigue	2.6±2.6 (0–9)	4.4±2.9 (0–10)
Poor sleep	2.7±2.8 (0–10)	2.6±2.8 (0–10)
Nausea	0.2±0.6 (0–3)	1.2±1.9 (0–8)
Overall well-being	2.5±2.3 (0–7)	3.6±2.5 (0–10)

Table II shows the symptom severity. The highest mean scores were reported for pain in activity (3.2) and dry mouth (3.1). Regarding anxiety, sadness/depression and sleep, the corresponding scores were 1.5, 1.2 and 2.7, respectively. Compared to the previous study, no significant increases were found. Most items had numerically lower mean values (anxiety 1.5 *vs.* 2.7, sadness/depression 1.2 *vs.* 2.1), whereas sleep quality was practically identical (2.7 *vs.* 2.6). The fatigue score was the only one with statistically significant difference, namely a reduction from the previous value (2.6 *vs.* 4.4, *p*=0.03).

Both study populations had comparable median age (70.5 *vs.* 70 years), gender distribution (62 *vs.* 74% male) and proportion of patients with bone metastases (54 *vs.* 62%). However, there were two significant imbalances, namely the proportion of patients with prostate cancer (12% *vs.* 30%, *p*=0.02) and breast cancer (0% *vs.* 12%, *p*=0.02).

Discussion

The ESAS tool has a long track record in the context of palliative radiotherapy and has demonstrated its usefulness in several studies (8–13). Patient-reported symptoms can be addressed and managed by care providers in a rapid and comprehensive fashion. Both prognosis and symptom burden should be assessed rigorously in order to personalize palliative radiotherapy, or select different palliative options, if indicated (14–16). In the present study, the symptom burden reported by patients during the early phase of the COVID-19 pandemic was analyzed. We were worried about increased symptom severity and used a previous database as a benchmark. Unexpectedly, no significant increases were found. Whereas sleep quality was practically identical, anxiety and sadness/depression were slightly reduced.

Several possible explanations for this exist. These include a shift in patients' baseline characteristics, *e.g.* age, treatment indication or disease extent. Older and sicker patients are expected to experience worse symptoms. Furthermore, previous studies have revealed associations between certain tumor types and higher frequencies of anxiety and depression. It has been shown that patients with head and neck, lung, pancreatic and breast cancer were at higher risk of depression. An increased prevalence of anxiety was reported in patients with thyroid, breast, pancreatic and gynecological cancer. Another relevant finding was the fact that patients with prostate cancer were reported to suffer from lower rates of depression and anxiety. In addition, men in general, *i.e.* irrespective of tumor type, have been found to under-report their symptoms (17-19). The present study included a lower proportion of patients with prostate cancer, potentially leading to higher scores of depression and anxiety. However, this was not observed in our study.

Alternatively, lower ESAS scores may be the result of patient preferences. If extremely worried and anxious patients chose to avoid radiotherapy during the pandemic, the remaining patients who showed up reported relatively modest ESAS scores. In this context, it must be noted that the ESAS is a simple tool and that more advanced and comprehensive assessments may result in a different picture. Nevertheless, it appears unlikely that completely different trends would be observed. Another important point is the regional impact that the COVID-19 pandemic actually has. The study was performed in a healthcare region called Nordland county, which has approximately 243,000 inhabitants. This rural part of Norway has seen a comparatively low number of people with COVID-19 infections. Until 31st of August 2020, 110 cases had been registered and there were no reported deaths due to infection. The intensive care resources were fully sufficient to handle all hospitalized patients (20). As a consequence of these favorable circumstances, oncology care has largely continued as planned after necessary precautions, such as procedures for testing and quarantine, had been implemented. This factor possibly explains why the observed ESAS scores had not increased and were still a reflection of the cancer burden without an added COVID-19 component. Vastly different levels of stress and symptom burden have been reported in cancer patients from other regions of the world (6). Baffert *et al.* reported a prospective observational study assessing patient-reported outcomes, quality of life and satisfaction with medical care (21). The participants were patients with cancer who attended a day hospital during the time period of May to June 2020 (21). The authors utilized the Generalised Anxiety Disorder Screener and 12-Item Short-Form Health Survey. Out of 267 patients, 189 completed the survey. As in our study, the patients had low anxiety scores, with only 11% showing anxiety. In a different study, patients with gynecological cancer were found to be concerned about sub-optimal care rather than the risk of COVID-19 infection (22). These patients reported significant anxiety about

progression of their disease resulting from modifications of oncological care related to the COVID-19 measures. Despite the associated risks, they wished to pursue and continue their treatment as originally planned. Only 17.5% were more afraid of COVID-19 than their cancer condition. The latter results correspond to those of the present study but comparison is hampered by different oncology settings, methods and tools, and questions asked. In addition, patient concerns and anxiety might also fluctuate in parallel with the variable number of infected people in a geographical region. The full picture of the present state of oncology has yet to unfold.

Like other previous retrospective studies, the present one must be regarded as hypothesis-generating. In addition, it is hampered by the limited number of patients, although statistical assumptions were considered. No longitudinal follow-up of ESAS after radiotherapy or more detailed questionnaires describing anxiety, depression and other symptoms were available. On the other hand, limited data related to palliative radiotherapy and patient-reported symptoms during the COVID-19 pandemic are available. Given that palliative radiotherapy is an important treatment modality, which can prolong survival in subgroups of patients, in addition to providing symptom improvement (23-25), efforts are necessary to ensure continued access.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

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

References

- 1 Guckenberger M, Belka C, Bezjak A, Bradley J, Daly ME, DeRuysscher D, Dziadziuszko R, Faivre-Finn C, Flentje M, Gore E, Higgins KA, Iyengar P, Kavanagh BD, Kumar S, Le Pechoux C, Lievens Y, Lindberg K, McDonald F, Ramella S, Rengan R, Ricardi U, Rimner A, Rodrigues GB, Schild SE, Senan S, Simone CB 2nd, Slotman BJ, Stuschke M, Videtic G, Widder J, Yom SS and Palma D: Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An astro-astro consensus statement. *Int J Radiat Oncol Biol Phys* 107(4): 631-640, 2020. PMID: 32589990. DOI: 10.1016/j.ijrobp.2020.05.012
- 2 Slotman BJ, Lievens Y, Poortmans P, Cremades S, Rengan R, Wakefield DV and Ricardi U: Effect of COVID-19 pandemic on practice in European radiation oncology centers. *Radiother Oncol* 150: 40-42, 2020. PMID: 32544604. DOI: 10.1016/j.radonc.2020.06.007
- 3 Jereczek-Fossa BA, Pepa M, Marvaso G, Bruni A, Buglione di Monale E, Bastia M, Catalano G, Filippi AR, Franco P, Gambacorta MA, Genovesi D, Iatì G, Magli A, Marafioti L, Meattini I, Merlotti A, Mignogna M, Musio D, Pacelli R, Pergolizzi S, Tombolini V, Trovò M, Ricardi U, Magrini SM, Corvò R, Donato V and AIRO

- (Italian Association of Radiotherapy and Clinical Oncology): COVID-19 outbreak and cancer radiotherapy disruption in Italy: Survey endorsed by the Italian association of radiotherapy and clinical oncology (AIRO). *Radiother Oncol* 149: 89-93, 2020. PMID: 32413527. DOI: 10.1016/j.radonc.2020.04.061
- 4 Achard V, Aebersold DM, Allal AS, Andratschke N, Baumert BG, Beer KT, Betz M, Breuneval T, Bodis S, de Bari B, Förster R, Franzetti-Pellanda A, Guckenberger M, Herrmann E, Huck C, Khanfir K, Matzinger O, Peguret N, Pesce G, Putora PM, Reuter C, Richetti A, Vees H, Vrieling C, Zaugg K, Zimmermann F, Zwahlen DR, Tsoutsou P and Zilli T: A national survey on radiation oncology patterns of practice in Switzerland during the COVID-19 pandemic: Present changes and future perspectives. *Radiother Oncol* 150: 1-3, 2020. PMID: 32512075. DOI: 10.1016/j.radonc.2020.05.047
 - 5 Sigorski D, Sobczuk P, Osmola M, Kuć K, Walerzak A, Wilk M, Ciszewski T, Kopeć S, Hryń K, Rutkowski P, Stec R, Szczylik C and Bodnar L: Impact of COVID-19 on anxiety levels among patients with cancer actively treated with systemic therapy. *ESMO Open* 5(5): e000970, 2020. PMID: 33097653. DOI: 10.1136/esmoopen-2020-000970
 - 6 Miaskowski C, Paul SM, Snowberg K, Abbott M, Borno H, Chang S, Chen LM, Cohen B, Hammer MJ, Kenfield SA, Kober KM, Levine JD, Pozzar R, Rhoads KF, Van Blarigan EL and Van Loon K: Stress and symptom burden in oncology patients during the COVID-19 pandemic. *J Pain Symptom Manage* 60(5): e25-e34, 2020. PMID: 32889039. DOI: 10.1016/j.jpainsymman.2020.08.037
 - 7 Vanni G, Materazzo M, Pellicciaro M, Ingallinella S, Rho M, Santori F, Cotesta M, Caspi J, Makarova A, Pistolese CA and Buonomo OC: Breast cancer and COVID-19: the effect of fear on patients' decision-making process. In *Vivo* 34(3 Suppl): 1651-1659, 2020. PMID: 32503825. DOI: 10.21873/in vivo.11957
 - 8 Nieder C, Kämpe TA, Pawinski A and Dalhaug A: Patient-reported symptoms before palliative radiotherapy predict survival differences. *Strahlenther Onkol* 194(6): 533-538, 2018. PMID: 29344766. DOI: 10.1007/s00066-018-1259-5
 - 9 Nieder C and Kämpe TA: Does marital status influence levels of anxiety and depression before palliative radiotherapy? In *Vivo* 32(2): 327-330, 2018. PMID: 29475916. DOI: 10.21873/in vivo.11241
 - 10 Nieder C and Kämpe TA: Contribution of patient-reported symptoms before palliative radiotherapy to development of multivariable prognostic models. *Anticancer Res* 38(3): 1705-1709, 2018. PMID: 29491105. DOI: 10.21873/anticancer.12404
 - 11 Khan L, Kwong J, Nguyen J, Chow E, Zhang L, Culleton S, Zeng L, Jon F, Tsao M, Barnes E, Danjoux C, Sahgal A and Holden L: Comparing baseline symptom severity and demographics over two time periods in an outpatient palliative radiotherapy clinic. *Support Care Cancer* 20(3): 549-555, 2012. PMID: 21360036. DOI: 10.1007/s00520-011-1120-1
 - 12 Lien K, Zeng L, Zhang L, Nguyen J, Di Giovanni J, Popovic M, Jamani R, Cramarossa G, Culleton S and Chow E: Predictive factors for well-being in advanced cancer patients referred for palliative radiotherapy. *Clin Oncol (R Coll Radiol)* 24(6): 443-451, 2012. PMID: 22794326. DOI: 10.1016/j.clon.2012.01.004
 - 13 Goyal UD, Riegert K, Davuluri R, Ong S, Yi SK, Dougherty ST and Hsu CC: Prospective study of use of edmonton symptom assessment scale versus routine symptom management during weekly radiation treatment visits. *JCO Oncol Pract* 16(9): e1029-e1035, 2020. PMID: 32384015. DOI: 10.1200/JOP.19.00465
 - 14 Nieder C, Norum J, Dalhaug A, Aandahl G and Pawinski A: Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. *Clin Exp Metastasis* 30(6): 723-729, 2013. PMID: 23392634. DOI: 10.1007/s10585-013-9573-x
 - 15 Nieder C, Angelo K, Dalhaug A, Pawinski A, Haukland E and Norum J: Palliative radiotherapy during the last month of life: Predictability for referring physicians and radiation oncologists. *Oncol Lett* 10(5): 3043-3049, 2015. PMID: 26722287. DOI: 10.3892/ol.2015.3656
 - 16 Nieder C, Andratschke NH and Grosu AL: Re-irradiation for recurrent primary brain tumors. *Anticancer Res* 36(10): 4985-4995, 2016. PMID: 27798857. DOI: 10.21873/anticancer.11067
 - 17 Parker P, Baile W, Moor C and Cohen L: Psychosocial and demographic predictors of quality of life in a large sample of cancer patients. *Psycho-Oncology* 12(2): 183-193, 2018. DOI: 10.1002/pon.635
 - 18 Brintzenhofe-szoc K, Levin T, Li Y, Kissane D and Zabora J: Mixed anxiety/depression symptoms in a large cancer cohort: Prevalence by cancer type. *Psychosomatics* 50(4): 383-391, 2019. DOI: 10.1176/appi.psy.50.4.383
 - 19 Miller K and Massie M: Depression and anxiety. *The Cancer Journal* 12(5): 388-397, 2020. DOI: 10.1097/00130404-200609000-00008
 - 20 Nieder C, Haukland EC, Mannsaker B and Yobuta R: Palliative radiotherapy during the last month of life: Have COVID-19 recommendations led to reduced utilization? In *Vivo* 35(1): 649-652, 2021. PMID: 33402522. DOI: 10.21873/in vivo.12304
 - 21 Baffert KA, Darbas T, Lebrun-Ly V, Pestre-Munier J, Peyramaure C, Descours C, Mondoly M, Latrouite S, Bignon E, Nicouleau S, Geyl S, Leobon S and Deluche E: Quality of life of patients with cancer during the COVID-19 pandemic. In *Vivo* 35(1): 663-670, 2021. PMID: 33402524. DOI: 10.21873/in vivo.12306
 - 22 Gultekin M, Ak S, Ayhan A, Strojna A, Pletnev A, Fagotti A, Perrone AM, Erzenoglu BE, Temiz BE, Lemley B, Soyak B, Hughes C, Cibula D, Haidopoulos D, Brennan D, Cola E, van der Steen-Banasik E, Urkmez E, Akilli H, Zapardiel I, Tóth I, Sehouli J, Zalewski K, Bahremand K, Chiva L, Mirza MR, Papageorgiou M, Zoltan N, Adámková P, Morice P, Garrido-Mallach S, Akgor U, Theodoulidis V, Arik Z, Steffensen KD and Fotopoulou C: Perspectives, fears and expectations of patients with gynaecological cancers during the COVID-19 pandemic: A Pan-European study of the european network of gynaecological cancer advocacy groups (ENGAGe). *Cancer Med* 10(1): 208-219, 2021. PMID: 33205595. DOI: 10.1002/cam4.3605
 - 23 Nieder C, Pawinski A, Haukland E, Dokmo R, Phillipi I and Dalhaug A: Estimating need for palliative external beam radiotherapy in adult cancer patients. *Int J Radiat Oncol Biol Phys* 76(1): 207-211, 2010. PMID: 19362788. DOI: 10.1016/j.ijrobp.2009.01.028
 - 24 Nieder C, Dalhaug A, Pawinski A, Haukland E, Mannsaker B and Engljähringer K: Palliative radiotherapy with or without additional care by a multidisciplinary palliative care team in patients with newly diagnosed cancer: A retrospective matched pairs comparison. *Radiat Oncol* 10: 61, 2015. PMID: 25889414. DOI: 10.1186/s13014-015-0365-0
 - 25 Nieder C, Angelo K, Haukland E and Pawinski A: Survival after palliative radiotherapy in geriatric cancer patients. *Anticancer Res* 34(11): 6641-6645, 2014. PMID: 25368269.

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