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Research article

Patient reported upper gastro-intestinal symptoms associated with fractionated image-guided conformal radiotherapy for metastatic spinal cord compression

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ABSTRACT

Background and purpose: Palliative radiotherapy is given to sustain or improve quality of life for patients with advanced cancer. Radiotherapy may however result in symptomatic side effects, which may affect the patient negatively. This prospective longitudinal study of 30 patients aimed at investigating the incidence and severity of early toxicity, particularly focusing on dysphagia, esophagitis and mucositis, following fractionated radiotherapy for cervical and thoracic metastatic spinal cord compression (MSCC), as well as determining the relationship between esophageal dose and early upper gastro-intestinal symptoms.

Materials and methods: Thirty patients receiving radiotherapy of 3Gyx10 for MSCC were included in the study. Patients were assessed for a total of 7 weeks from onset of radiotherapy using the Edmonton Symptom Assessment System (ESAS) questionnaire. Upper gastro-intestinal symptoms and severity were assessed from the tenth and eleventh question section of the ESAS questionnaire of "other problems" and how much this affected them. The relationships between the mean and maximum esophageal doses and incidence of dysphagia, esophagitis or mucositis were estimated and dose response curves determined.

Results: Eleven patients reported esophageal symptoms (average duration eleven days, range 1–18 days). Incidence of esophageal toxicity in patients treated at Th8 or above was 79 percent, while no patients treated below Th8 reported any symptoms ($p < 0.001$). Furthermore, 2 out of 3 patients irradiated at the cervical region reported substantial changes in taste sensation.

Risk of symptoms correlated with both mean and maximum esophageal dose and may be a useful tool in planning radiotherapy for MSCC, potentially reducing early upper gastro-intestinal toxicity.

Introduction

Five to ten percent of cancer patients experience symptomatic compression of the spinal cord or the cauda equina from metastatic disease (metastatic spinal cord compression, MSCC) [1]. Symptoms of MSCC include severe neuropathic pain and other neurological symptoms including motor dysfunction and weakness, numbness and bladder or bowel dysfunction [2]. It is a disabling complication, which untreated will further the complication of these symptoms and may lead to paralysis, loss of medullar function distally from the compression and incontinence [3,4].

Life expectancy is typically short at the time of MSCC diagnosis, with a 1-year survival rate of ~30% [5]. Interventions for MSCC mainly aim at improving quality of life (QoL), through pain control and by maintaining or improving functional capacity.

Early detection and rapid onset of treatment are key elements for improved outcomes. Pre-treatment ambulatory function and time of developing motor symptoms are the primary predictors of post-treatment functional outcomes [6]. Thus, patients with lower-extremity function and sensation at the onset of treatment have better prognosis for maintaining their functional independence and longer survival time [7].

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Treatment options include decompressive surgery, corticosteroids and radiotherapy (RT), or a combination of these, with RT being one of the key treatment modalities offered for MSCC [2]. Patients may, however, experience early toxicity from the RT, which paradoxically may affect their well-being and contribute to a decline in their QoL. Previous studies investigating adverse effects found early toxicity related to RT for MSCC to include gastro-intestinal toxicity, mucositis, bone-marrow suppression, and myelopathy, depending on the level of the irradiated spine [1,8]. However, none of these studies have systematically and specifically investigated early toxicity related to incidental irradiation of the esophagus.

Mucositis is a known side effect of radiotherapy in head and neck cancers [9]. When investigating radiotherapy-related toxicity, the focus is often on toxicity of the Common Terminology Criteria for Adverse Events grade 3 or above. However, due to the short life expectancy [3] and the primary QoL-focused treatment intent for these palliative patients, it is highly relevant to investigate milder toxicity as well. Milder toxicity might still have significant impact on the patient's well-being, and particularly mucositis in the gastro-intestinal tract could be unappreciated and underreported. This is supported by anecdotal reports from patients having previously been irradiated for MSCC at the level of the esophagus. The toxicity of the treatment may be measured using various approaches; one of the most preferred methods is patient reported outcome measures [10]. This allows patients to report self-experienced symptoms, providing a patient-focused perspective of adverse events.

In this prospective longitudinal study, we aimed at investigating the patient-reported incidence and severity of symptoms, particularly focusing on dysphagia, esophagitis and mucositis following fractionated RT for MSCC, and its relationship with dose to the esophagus.

Materials & methods

This prospective study included 30 consecutively treated patients with advanced cancer receiving fractionated RT for MSCC at the Department of Oncology, Rigshospitalet, Denmark. Patients with a minimum life expectancy of 6 months were eligible for the study if they were prescribed moderately hypo-fractionated radiotherapy (30 Gy in 10 fractions) for MSCC, which is local hospital standard for patients with a life expectancy of 6 months or above to ensure tumor control, and had not previously received irradiation to the site in question [2,11]. General performance status was based on the ECOG performance status and life expectancy was based on the Tokuhashi score [12]. The target was defined as the entire involved vertebrae including the relevant spinous processes, with a 5 mm planning target volume (PTV) margin. For organs at risk (OARs), arms, kidneys and small bowel for caudal target volumes were outlined as part of the treatment planning process, as well as the spinal cord to avoid hotspots within the spinal cord. For arms the maximum dose (D_{max}) was 3 Gy and as low as possible for other OARs. Currently there are no local hospital recommendations for OAR delineation of the esophagus or lungs for MSCC prior to treatment planning. The entire esophagus, from the cricoid to the gastro-esophageal junction was retrospectively delineated for all patients [13].

Patients were planned with the Eclipse™ planning system (Varian Medical Systems, Palo Alto, CA, USA) calculated using Acuros XB® (version 13.6) and subsequently treated with simple single arc volumetric modulated arc therapy (VMAT). Multiple targets per patient were also allowed. Patients were treated five days a week with daily cone beam computed tomography (CBCT) image guidance.

Assessment

The Edmonton Symptom Assessment System (ESAS) is developed to screen nine symptoms in patients with advanced cancer on numerical scales (NRS)(scale 0–10). In the ESAS, patients rate the severity of the following nine symptoms: pain, activity, nausea, depression, anxiety, drowsiness, lack of appetite, well-being, and shortness of breath on a 10-cm line. The sum of patient responses to these nine symptoms is the ESAS distress score. Further, the questionnaire adds an optional tenth symptom, which can be added by the patient. This tenth symptom allows for the opportunity for patients to add an additional symptom, which clinicians may not have considered. The ESAS has well-established reliability and validity as a routine self-assessment tool in patients with advanced cancer [14].

On the first day of treatment, baseline data were acquired prior to RT delivery. Patients filled in the ESAS questionnaire and their answers were recorded by a radiation therapy technologist or radiation therapy nurse at the clinic for the initial 3 weeks and weekly for the remaining 4 weeks. Thus, patients were followed for 7 weeks in total, or until they either could no longer cooperate or decided to leave the study.

Patients reported their symptoms according to ESAS to an RT technologist or RT nurse. Further, patients were interviewed either in the clinic, after each RT fraction, or by phone post-treatment.

The incidence of dysphagia, esophagitis and/or mucositis was determined from the patient responses on the optional tenth symptom in the ESAS titled "Other problem", where patients were asked if they experienced any symptoms not mentioned in the above questions", where patients were given the opportunity to self-report any adverse effects. Since early toxicity typically emerged after the first week following RT, patients who were not followed for at least 7 days were excluded from the current analysis. Any level of dysphagia, esophagitis and/or mucositis was recorded, irrespective of severity. The severity of the early toxicity was estimated based on the question following the tenth optional symptom in the ESAS questionnaire: "How much does this affect you?". The severity was based on a scale of 0–10, where 0 was not affected and 10 was worst imaginable. The patient's reported answers were collected.

Ethics

Approval was obtained from the regional research ethics committee (Reg. no. 49984) and the Danish data protection agency, and all patients provided oral and written informed consent for study participation.

Statistics

Basic descriptive statistics were used to report patient characteristics, and incidence and average duration of early toxicity were established based om patient self-report.

The severity of the early toxicity was recorded as the highest patient self-reported score, based on the patient's self-reporting of how much the toxicity affected them and an average value was calculated.

The incidence of dysphagia, esophagitis or mucositis in patients with at least one treated vertebra at Th8 or above was compared to the incidence for patients treated below Th8 only, using Fisher's exact test. The relationship between the mean (D_{mean}) and D_{max} esophageal doses and incidence of dysphagia, esophagitis or mucositis were examined using the Wilcoxon rank sum test, comparing distributions of dose metrics in the two groups. Dose-response curves for the mean and maximum esophagus doses were

estimated using univariate logistic regression. A p-value < 0.05 was used as level of significance.

Results

Thirty patients (12 women / 18 men) participated in the study. Four patients were excluded from this analysis due to change in fractionation (one patient) or inability to complete questionnaires beyond the week one assessment (three patients). Patient characteristics can be viewed in Table 1.

Out of the 26 patients, 11 reported treatment-related toxicity of the gastrointestinal tract (Fig. 1); the average duration of the adverse symptoms was 11 days (range 1–18 days). All patients reporting dysphagia, esophagitis or mucositis were treated at Th8 or above 11/14 (79%); while no patients treated below Th8 reported any symptoms (0/12, p < 0.001). Furthermore, 2 out of 3 patients irradiated at the cervical region reported substantial changes in taste sensation. Out of the 11 patients reporting early toxicity of the upper gastro-intestinal tract, 10 patients rated the severity. The average rating of how much the toxicity affected the patients was 4.4 (range 2–7) (Fig. 2).

The median D_{mean} was 7.7 Gy (range 0.1–15.9 Gy) for patients reporting dysphagia, esophagitis and/or mucositis, and 0.2 Gy (0.0–10.8 Gy) for patients not reporting these toxicities, respectively (p = 0.004). Corresponding values for D_{max} were 30.4 Gy (1.1–31.3 Gy) for those reporting dysphagia, esophagitis or mucositis and 0.5 Gy (0.0–31.4 Gy) for those without these toxicities, respectively (p = 0.009).

Dose response curves, as estimated using univariate logistic regression, for mean and maximum dose to the esophagus are shown in Fig. 3; with summary data points added for illustration of model fit. A change in mean dose of 1 Gy corresponded to an estimated odds ratio (OR) for developing toxicity of the gastro-intestinal tract of 1.38 (95% confidence interval 1.09–1.76). OR for a change in maximum dose of 1 Gy was 1.11 (1.03–1.20).

Discussion

This prospective longitudinal study aimed at investigating the patient-reported incidence and severity of symptoms, following fractionated RT for MSCC, and its relationship with dose to the esophagus.

In this prospective consecutive study of early toxicity for patients receiving RT for MSCC, we observed a high incidence of dysphagia, esophagitis and mucositis, and a strong correlation between treatment site and occurrence of this RT-related toxicity.

Table 1
Patient characteristics of the 26 patients included in the final analysis.

	Median	*Range*
Age (y)	65	39–84
Treated vertebra (n)	2	1–9
	n	*%*
Sex		
Male	15	58
Female	11	42
Primary disease		
Prostate	6	23.1
Breast	4	15.4
Gynecological	3	11.5
Lung	2	7.7
Esophagus	2	7.7
Unknown primary tumor	2	7.7
Gastroesophageal junction	2	7.7
Neuroendocrine tumor	2	7.7
Other	3	11.5

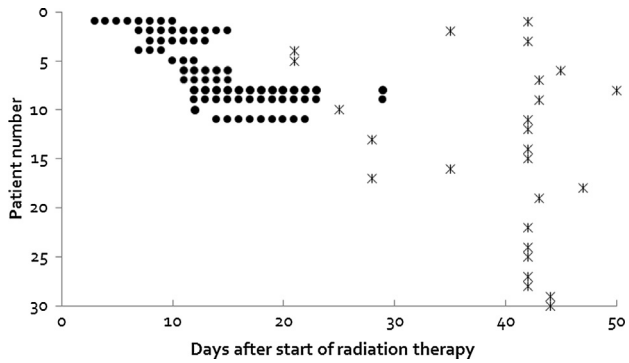

Fig. 1. Overview of patient-reported dysphagia, esophagitis or mucositis in the days following RT for MSCC, represented in order of when toxicity was reported. The days where the patients reported toxicity of the gastro-intestinal tract are indicated with solid black circles ●. The patients are represented in order of first experienced toxicity (not study enrolment). End of follow-up is marked with a star ✳.

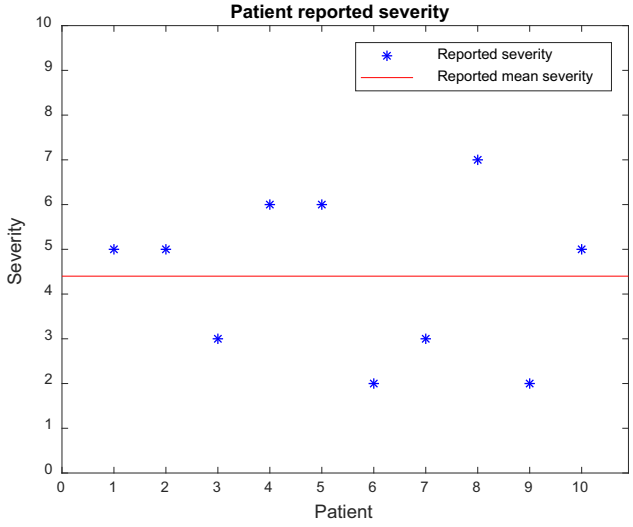

Fig. 2. Shows the patients' self-evaluation of how dysphagia, esophagitis or mucositis affected them on a scale of 0–10, where 0 is not affected and 10 is highest possible. Patients' self-evaluation ranged from 2-7, with a mean value of 4, 4. 10 out of 11 patients reporting upper gastro-intestinal symptoms reported the severity of these symptoms. Patients are represented in the order of first experienced symptoms.

Previous studies investigating adverse effects and toxicity of RT have not focused mainly on the acute toxicity, but on the treatment efficacy in comparing treatments or treatment regimens [1,8,15,16]. Fractionation schemes and reporting methods, outcomes, as well as patient follow-up vary considerably between studies, which can make comparison of toxicity reporting difficult.

In contrast to previous studies, which typically have measured toxicity ≥ grade 3, this study included any type and severity of patient reported symptoms. This may be a contributing factor to the high incidence of symptom reporting in this study. However, as these patients have a short remaining life span and the intent of RT for MSCC is to improve QoL through pain control and by maintaining or improving of functional capacity, we find it highly relevant to investigate any toxicity, which may have a physical or psychological effect on the patient's well-being.

In a report on 1304 MSCC patients, Rades et al found only grade 1 early toxicity and no late toxicity [1]. In a study of 149 patients treated stereotactically, Wang et al reported the following grade 3 toxicities: dysphagia (one), neck pain (one), pain associated with severe tongue edema and trismus (two) [15]. In another study of

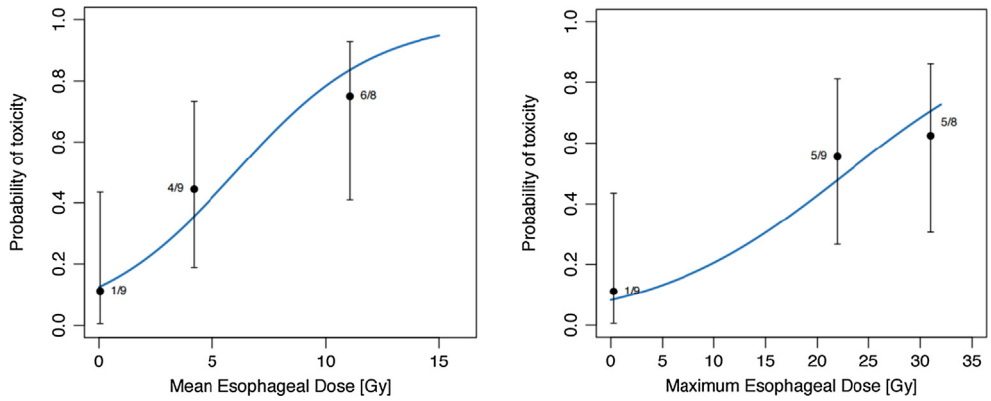

Fig. 3. The risk of toxicity of the gastro-intestinal tract as a function of mean and maximum esophageal dose, as estimated using univariate logistic regression. Model coefficients were $b_0 = -1.953$ (95% CI -3.534 – -0.371), $b_{mean} = 0.324$ (0.085 – 0.564) and $b_0 = -2.414$ (-4.522 – -0.307), $b_{mean} = 0.106$ (0.026 – 0.186) for the estimates of mean and max dose, respectively. Data points with 95% confidence intervals are added for illustration only, and represent all patients separated into 3 bins.

324 patients, Rades et al found no early radiation-related toxicity above grade 1 using the National Cancer Institute Common Toxicity Criteria, and no late toxicity [16]. In a study of 276 patients, Maranzano et al found very few cases of grade 3 esophagitis or laryngitis (1,5% of the patients) [8]. Unlike our study, patient follow-up in these studies occurred at varying time points, typically with months apart. Rades et al assessed the patients prior to initiation of RT, as well as 1, 3 and 6 months after RT [1]. Wang et al measured baseline as well as 3 and 6 months after RT [15]. Maranzano followed the patients "before and after RT", and once monthly [8]. In this study we used the ESAS questionnaire as a validated questionnaire in patients with cancer for symptoms screening. This was chosen due to palliative intent of treatment in patients with advanced cancer. Other questionnaires have been used in different settings depending on the context of treatment. A PRO questionnaire does not access causality of symptoms but throughout objective assessment by physician during and after treatment would be burdensome and require additional clinical visit. The PRO-CTCAE has been used to access similar symptoms of dysphagia in patients undergoing chemoradiotherapy for head & neck cancer. This study found a disagreement of symptoms reported by patient with lower severity reported by physician assessment [17]. Such a disagreement also exists comparing the symptoms reported in current study with a low incidence of treatment related symptoms in the studies mentioned above.

Generally, symptomatic gastro-intestinal toxicity in our study was first observed about one week after initiation of RT and had a typical duration of 1–2 weeks (median duration 11 days). Because early toxicity, as shown in our results, may be of short duration, and because patients may not report a transient toxicity at follow-up sessions occurring 1, 3 and 6 months after RT, the incidence of oral and esophageal toxicity may have been underestimated in the literature.

Additionally, some patients reporting symptoms in this study considered these not to be toxicity related symptoms, but due to tumor growth, which in a couple of patients in this study created additional and unnecessary anxiety, depression and grief for themselves and their families. The causes of the symptoms were explained and resolved during follow-up sessions in our study; however, this misconception may likely add to the underreporting of toxicity symptoms.

In contrast to previous studies, we found that gastro-intestinal toxicity following palliative RT for MSCC may occur in a substantial proportion of patients for whom the target is situated at the level of the esophagus. This study showed no patients experiencing symptoms below the level of TH8, which typically is situated just above the gastro-intestinal junction. Due to the surprising results of this optional tenth point in the ESAS questionnaire, further enquiries about the experienced upper gastro-intestinal symptoms of these patients were not made systematically. However, further investigations to clarify these symptoms, duration and severity in a larger population should be conducted.

In order to support this patient group in dealing with these potential toxicities, we suggest that patients undergoing RT for MSCC at the level of the upper or central part of the thoracic spine or above should be timely informed that they can expect to experience gastro-intestinal toxicity as well as a change in taste sensation, which likely will last up to 3 weeks. This may help to reduce worries and anxiety for the patients, as well as give them a better base of informed consent for this treatment. Several patients in this study reported not to have been properly informed about these potential toxicities pre-treatment. This study, however, bases on a small patient group and further studies regarding patient reported esophageal toxicity should be performed to further verify and clarify these findings and their clinical significance for the patient-reported outcomes.

Furthermore, if the RT is delivered using VMAT, it may be possible to optimize treatment plans to reduce dose to the esophagus and oral cavity. Our limited data indicate that there may exist a dose–response relationship for gastro-intestinal toxicity of the esophagus and oral cavity, justifying a rationale for further dose plan optimization.

Finally, it should be noted that these patients underwent a fractionation scheme of 30 Gy in 10 fractions. The optimal fractionation schedule for this patient population is still under debate and toxicities may vary in this patient group depending on the chosen fractionation scheme.

In conclusion, in this prospective study of 30 patients, 79% of patients who received RT for MSCC for the cervical and upper thoracic spinal column experienced toxicity of the gastro-intestinal tract. All patients stated that this toxicity affected them. This preliminary data is contrasting previously published findings, most likely due to the inclusion of all types and intensity levels of toxicity, as well as a much earlier and more frequent follow-up assessments compared to former studies. A dose-response relationship for RT of the esophagus may exist and could be a useful tool in planning of RT for MSCC, potentially reducing the incidence of toxicity of the gastro-intestinal tract.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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