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ORIGINAL ARTICLE

Prevalence of oral mucositis, dry mouth, and dysphagia in advanced cancer patients

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Abstract
Background Oral symptoms can be a sign of an underlying systemic condition and have a significant impact on quality of life, nutrition, and cost of care, while these lesions are often studied in the context of cancer treatment. However, information regarding oral symptoms in advanced cancer patients is poor. The aim of this multicenter study was to determine the prevalence and the characteristics of oral symptoms in a large population of advanced cancer patients.
Methods A consecutive sample of patients with advanced cancer for a period of 6 months was prospectively assessed for an observational study. At time of admission, the epidemiological characteristics, surgery-radiotherapy of head and neck, and oncologic treatments in the last month were recorded. The presence of mucositis, dry mouth, and dysphagia was assessed by clinical examination and patients' report and their intensity recorded. Patients were also asked whether they had limitation on nutrition of hydration due to the local condition.
Results Six hundred sixty-nine patients were surveyed in the period taken into consideration. The mean age was 72.1 years (SD 12.3), and 342 patients were males. The primary tumors are listed in Table 1. The prevalence of mucositis was 22.3 %. The symptom relevantly reduced the ingestion of food or

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fluids and was statistically associated with the Karnofsky level and head and neck cancer. The prevalence of dry mouth was 40.4 %, with a mean intensity of 5.4 (SD 2.1). Several drugs were concomitantly given, particularly opioids (78 %), corticosteroids (75.3 %), and diuretics (70.2 %). Various and non-homogeneous treatments were given for dry mouth, that was statistically associated with current or recent chemotherapy, and hematological tumors. The prevalence of dysphagia was 15.4 % with a mean intensity of 5.34 (SD 3). Dysphagia for liquids was observed in 52.4 % of cases. A high level of limitation for oral nutrition due to dysphagia was found, and in 53.4 % of patients, alternative routes to the oral one were used. Dysphagia was statistically associated with the Karnofsky level and head and neck cancer. A strong relationship between the three oral symptoms was found.

Conclusion In advanced cancer patients, a range of oral problems significantly may impact on the physical, social, and psychological well-being of advanced cancer patients to varying degrees. These symptoms should be carefully assessed early but become imperative in the palliative care setting when they produce relevant consequences that may be life-threatening other than limiting the daily activities, particularly eating and drinking.

Keywords Advanced cancer · Palliative care · Supportive care · Oral symptoms · Dry mouth · Mucositis · Dysphagia

Introduction

Although cancer treatments have improved over the last decades, a damage to the head and neck structures is frequently reported as an unwanted consequence, often due to cancer and noncancer therapies. Particularly, oral cavity complications may arise throughout and after cancer treatment and often encompass a series of oral symptoms such as mucositis, dry mouth, and dysphagia. Dry mouth or xerostomia refers to any condition in which your mouth is unusually dry. Most often, dry mouth is the result of a decrease in saliva produced by salivary glands, and it is frequently a side effect of medication or caused by a condition that directly affects the salivary glands [1, 2]. Mucositis is a mucosal injury with a complex pathogenesis involving all compartments, rather than just the epithelium. Mucositis is one of the most significant toxicities in cancer patients undergoing cytotoxic treatment. It can have a negative impact on both quality of life and health economics. Severe oral mucositis can contribute to hospitalization, need for narcotic analgesics, total parenteral nutrition, suboptimal delivery of antineoplastic treatment, and morbidity and mortality [3]. Dysphagia is a swallowing disturbance, due to many neuromuscular conditions and consequence of systemic weakness [4]. These symptoms range from mild disturbances to debilitating, painful conditions that have a marked impact on quality of life, compromise vital functions such as eating, and are potentially life-threatening. The pathophysiology of these oral symptoms is quite complex and variable along the course of disease and multiple mechanisms may overlap. Oral symptoms can be a sign of an underlying systemic condition and have a significant impact on quality of life, nutrition, and cost of care. For example, head and neck cancer patients are particularly at risk, due to disease localization and the need of local treatments. While these lesions are often studied in the context of cancer treatment and treatment guidelines have been provided [5], information regarding oral symptoms in advanced cancer patients is poor. The aim of this multicenter study was to determine the prevalence and the characteristics of oral symptoms in a large population of advanced cancer patients.

Patients and methods

A consecutive sample of patients with advanced cancer admitted to different settings (home care, palliative care unit, or hospice) for a period of 6 months was prospectively assessed for an observational study. Informed consent and institutional approval of University of Palermo were obtained. No specific inclusion-exclusion criteria were used, unless for patients unable to communicate. At time of admission, the epidemiological characteristics, surgery-radiotherapy of head and neck, and oncologic treatments performed in the last month were recorded. Karnofsky level, which is a well-validated scale of patients' function impairment, was assessed. The presence of mucositis, dry mouth, and dysphagia was assessed by clinical examination and patients' report.

Patients with mucositis were assessed according to WHO grading and Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients were asked whether they had limitation on nutrition of hydration due to the local condition and were receiving parenteral hydration or parenteral nutrition.

The intensity of dry mouth was graded on a numerical scale from 0 to 10, where 0 is the absence of the symptom and 10 is the maximum intensity a patient can imagine, reflecting the concept of Edmonton Symptoms Assessment Scale (other symptoms). There were also recorded drugs possibly influencing dry mouth, drugs used for dry mouth, if any, and who prescribed them.

The intensity of dysphagia was graded on a numerical scale from 0 to 10, where 0 is the absence of the symptom and 10 is the maximum intensity a patient can imagine. Patients were also asked whether they had dysphagia to solids or liquids and had limitations in ingesting food or fluids, scoring on a scale from 0 (no limitation) to 4 (total limitation), were receiving parenteral hydration or nutrition or enteral nutrition due to dysphagia, and had limitations in swallowing drugs. The need

of using alternative route and which drugs were administered through this alternative route were also recorded.

Statistical analysis

The analysis addressed at first the prevalence structure of clinical variables, providing descriptive statistics and their sample distributions. Statistical association among symptoms was dealt with a χ^2 test, with a type I error set at 5 %, adjusted according to Sidak for multiple testing. The association strength was estimated by Cramer V. After the association was assessed, a χ^2 component analysis has been performed to device the influence of the variable outcomes. The odds ratios for mucositis, dry mouth, and dysphagia were estimated, according to cancer types, performing a logistic regression. Each odds ratio statistical significance was tested carrying out a Wald statistics. The analysis has been carried by the Statistical software STATA version 13.

Results

Six hundred sixty-nine patients were surveyed in the period taken into consideration. The mean age was 72.1 years (SD 12.3), and 342 patients were males. The primary tumors were in a rank order: gastrointestinal 243 (38 %), lung 134 (21 %), hematological 67 (10.5 %), breast 54 (8.4 %), gynecological 41 (6.4 %), urological 35 (5.5 %), prostate 20 (3.1 %), head-neck 20 (3.1 %), and others 55 (8.4 %). Previous treatments included chemotherapy 103 (15.4 %), or monotherapy 30 (4.5 %), targeted therapy 59 (8.8 %), and palliative care 476 (71.3 %).

Forty-three (6.4 %) and twenty-six (3.9 %) patients had received head and neck radiotherapy or surgery, respectively, and 192 patients (28.7 %) patients were receiving or had received chemotherapeutic agents in the last month.

Mucositis

The prevalence of mucositis was 22.3 % (149 patients). The WHO grading was G1=94 (63.1 %), G2=39 (26.2 %), and G3/G4=16 (10.7 %), and CTCAE grading was G1=68 (45.9 %), G2=57 (38.5 %), and G3/G4=23 (15.6 %).

The level of limitation in ingesting food or fluids due to mucositis is presented in Table 1. Mucositis was statistically associated with the Karnofsky level and head and neck cancer (see Table 2).

Dry mouth

The prevalence of dry mouth was 40.4 % (270 patients). The mean intensity was 5.4 (SD 2.1). Current drug medications included in a rank order: opioids (124 patients, 45.9 %), corticosteroids (107 patients, 39.6 %), diuretics (73 patients, 27 %), benzodiazepines (60 patients, 22.2 %), anticonvulsants (38 patients, 14.1 %), antidepressants (33 patients, 12.2 %), neuroleptics (28 patients, 10.4 %), nonsteroidal antiinflammatory drugs (17 patients, 6.3 %), and others (48 patients, 17.8 %).

Table 1 Limitations for ingesting food or fluids due to mucositis

Level of limitation	*n*	%
No limitations	58	38.9
Mucositis partially preventing nutrition or hydration	50	33.6
Mucositis severely limiting nutrition or hydration	32	21.5
Mucositis completely preventing nutrition or hydration	9	6

The medical treatment for dry mouth included chlorexidine (70 patients, 27.9 %), antifungal drugs (42 patients, 16.7 %), benzydamine (12 patients, 4.8 %), and different natural agents (20 patients, 8 %). The treatment was prescribed by oncologists (44.6 %), general practitioners (9.8 %), palliative care physicians (37.7 %), and others (7.9 %). Dry mouth was statistically associated with current or recent chemotherapy and hematological tumors (see Table 3).

Dysphagia

The prevalence of dysphagia was 15.4 % (103 patients). The mean intensity was 5.34 (SD3). Dysphagia for liquids was observed in 54 patients (52.4 %). The level of limitation for oral nutrition due to dysphagia is presented in Table 4. In 55 patients (53.4 %), alternative routes to the oral one were used

Table 2 Mucositis: odds ratio estimates adjusted by clinical covariates

Mucositis	Odds ratio	$P>\|z\|$	95 %	Confidence interval
Age	.9914167	0.323	.9746121	1.008511
Gender	.9286295	0.733	.6066685	1.421456
Karnofsky	.9737605	0.000	.9599187	.9878018
Head& neck surgery	.594968	0.416	.170468	2.07656
Head& neck radiotherapy	1.050387	0.914	.4311677	2.558895
Chemotherapy	1.500154	0.094	.9326549	2.412963
Ematological	1.102837	0.909	.2071616	5.871019
Breast	1.028553	0.972	.2084537	5.075091
Brain	1.609003	0.674	.1752023	14.77658
Gastrointestinal	1.559377	0.557	.3534324	6.880119
Gynecological	1.118285	0.893	.2202817	5.6771
Head-neck	6.313404	0.049	1.009488	39.48444
Urological	.8394596	0.843	.1478416	4.766536
Lung	2.452549	0.242	.5452766	11.03109
Melanoma	1.19927	0.853	.1746466	8.23519
Prostate	1.366397	0.745	.2079467	8.978462

Table 3 Dry mouth: odds ratio estimates adjusted by clinical covariates

Dry mouth	Odds ratio	$P>\|z\|$	95 %	Confidence interval
Age	.9935629	0.384	.9792142	1.008122
Gender	1.119819	0.546	.775804	1.616381
Karnofksy	.9951631	0.398	.9840281	1.006424
Head and neck surgery	.9445179	0.915	.3294495	2.707893
Head and neck radiotherapy	1.15019	0.732	.5162723	2.562479
Chemotherapy	1.476419	0.048	1.0784813	2.227753
Ematological	.230995	0.008	.0788427	.6767738
Breast	.4682747	0.185	.1525721	1.43723
Brain	.6320195	0.568	.1308484	3.052759
Gastrointestinal	.4788819	0.126	.1862802	1.231091
Gynecological	.6212908	0.418	.1962211	1.96718
Head and neck	1.316401	0.688	.3441341	5.035572
Urological	.4127433	0.127	.1324482	1.286217
Lung	.5071452	0.170	.1922816	1.337602
Melanoma	1.781293	0.445	.405108	7.832493
Prostate	1 (Collinear)			

Table 5 Dysphagia: odds ratio estimates adjusted by clinical covariates

Dysphagia	Odds ratio	$P>\|z\|$	95 %	Confidence interval
Age	1.013707	0.212	.9922551	1.035623
Gender	.9851031	0.953	.5965768	1.626661
Karnofsky	.9703302	0.001	.9532461	.9877205
Head and neck surgery	2.626915	0.135	.7402807	9.321711
Head and neck radiotherapy	1.258531	0.675	.4289219	3.692748
Chemotherapy	1.601041	0.108	.9018514	2.842301
Ematological	1.388562	0.706	.2516026	7.66329
Breast	1.105016	0.916	.1709858	7.141297
Brain	.697676	0.790	.0493851	9.856241
Gastrointestinal	2.17586	0.334	.4487684	10.54969
Gynecological	1.377164	0.744	.2018668	9.395214
Head and neck	17.17841	0.003	2.711599	108.8279
Urological	1.636422	0.591	.2711733	9.875153
Lung	1.802767	0.472	.3618019	8.982731
Melanoma	1.334474	0.792	.1567987	11.35738
Prostate	1 (Collinear)			

for administering opioids (61 %), diuretics (39.1 %), nonsteroidal antiinflammatory drugs (9.8 %), corticosteroids (53.7 %), benzodiazepines (26.8 %), gastroprotector (proton pump inhibitors or anti-H2 receptors agents) (46.3 %), antibiotics (7.3 %), anticholinergic drugs (14.6 %), antiemetics (21.9 %), neuroleptics (19.5 %), and others (9.8 %). Dysphagia was statistically associated with the Karnofsky level and head and neck cancer (see Table 5). Finally, a strong relationship between the three oral symptoms was found (see Table 6).

Discussion

This study has shown that oral symptoms are relevant in palliative care patients.

The prevalence of mucositis, dry mouth, and dysphagia was 22, 40, and 15 %, respectively. These symptoms strongly limited the ingestion of food and fluids and have deleterious effects in the process of care. A lower Karnofsky status, a recent or current treatment with chemotherapic agents, and head and neck cancer were strongly predictive at admission to different palliative care settings. These findings were expected, considering that most of these symptoms are often due to specific causes, individual conditions, or the consequences of disease progression.

Table 4 Limitations for oral nutrition due to dysphagia

Level of limitation	*n*	%
No limitations	12	11.6
Dysphagia partially preventing nutrition	44	42.7
Dysphagia severely limiting nutrition	36	34.9
Dysphagia completely preventing nutrition	11	10.7

Data in palliative care patients are really poor. It has been found that patients with head and neck cancer may experience a significant symptom burden even prior to radiation or chemotherapy. It has been reported that difficulty chewing, dry mouth, thick saliva, and pain were individual symptoms that were significantly associated with reduced dietary intake [6]. These symptoms also occur in outpatients receiving chemotherapy with cancers outside the head and neck region. In particular, dry mouth was reported in about 60 % of patients [7].

Mucositis

More than 20 % of advanced cancer patients admitted to different palliative care settings presented mucositis of various severity. In a relevant percentage of patients, about 60 %, the severity of this symptom limited the ingestion of fluid and liquids, with 40 % of patients having nutrition or hydration severely impaired. Mucositis is a highly feared and potentially debilitating toxicity associated with many cancer therapies, including concurrent chemoradiotherapy for patients with head and neck cancer and use of mucotoxic chemotherapeutic agents [8–10]. Severe oral mucositis can contribute to hospitalization, need for narcotic analgesics, total parenteral nutrition, suboptimal delivery of antineoplastic treatment, and

Table 6 Association of oral symptoms

	Dry mouth			Dysphagia		
Mucositis	No	Yes	*p*	No	Yes	*p*
No	347 (66.9 %)	172 (33.1 %)	0.00000	459 (88.4 %)	60 (11.6 %)	
Yes	51 (34.2 %)	98 (65.8 %)		106 (71.1 %)	43 (28.9 %)	0.00000
	Dysphagia					
Dry mouth	No	Yes	*p*			
No	364 (91.5 %)	34 (8.5 %)				
Yes	201 (74.4 %)	69 (25.6 %)	0.00000			

morbidity and mortality. This complication has a significant impact on patients' quality of life, morbidity and treatment outcome, as well as health care cost [5, 11]. The presence of oral mucosal damages may also be of concern in advanced cancer patients, but existing data are really lacking. In a clinical study including terminally ill patients with a limited life expectancy of 2–3 weeks, oral health conditions affected functional and social activities. Salivary hypofunction was present in almost patients, and signs of mucositis were also often reported. Finally, pain due to oral ulcerations had a higher social impact [12]. In this survey, this complication, other than been associated with head and neck cancer, was more frequent in patients with lower levels of Karnofsky status, when more complications due to previous damage, poor oral hygiene, infections, or local disease are likely to compromise the integrity of oral mucosa. Pain may be of concern, possibly limiting the ingestion of food and fluids. Sixteen percent of patients reported mouth pain at a mean intensity of 5.5 on a numerical scale from 0 to 10 [13]. As a consequence, oral cavity should be carefully assessed to treat the local condition, while eliminating eventual reversible factors, and pain management should be optimized.

Dry mouth

The prevalence and intensity of dry mouth were relevant, involving about 40 % of patients. Dry mouth was more likely to occur in patients with hematological tumors or receiving current or recent chemotherapy, despite the use of different therapies, prevalently prescribed by oncologists. This was possibly the consequence of the concomitant use of many drugs prescribed to this population. Dry mouth has been traditionally described in patients receiving radiotherapy for head and neck cancer, chemotherapy, or hematopoietic stem cell transplantation [14]. However, in outpatients receiving chemotherapy for cancers outside the head and neck region, dry mouth with a certain intensity was reported by 59 % of patients [7]. Dry mouth was one of the individual symptoms that was significantly associated with a reduced dietary intake [6]. Moreover, it is likely that in advanced cancer patients with a progression of disease and a low performance status, other factors, for example, the use of several drugs with a potential for producing dry mouth, may play an overlapping role. The causes most frequently assumed to be responsible in palliative care patients were ill-fitting dentures for mouth pain, medications, and possible oral fungal infections for mouth dryness [14]. In palliative care patients hospitalized on a medical ward, figures similar to present data were reported [15]. In patients attending a palliative care outpatient clinic, the prevalence of dry mouth was even higher to that reported in this survey [16]. Data were even more relevant in another study in which 88 % of palliative care patients reported dry mouth, with an intensity similar to that found in this study [13]. Dry mouth was one of the symptoms that presented a tendency to persist or to worse after admission to a palliative care unit [17]. This is consistent with other data showing that the prevalence of dry mouth was 25 and 61 % at admission and during the patients' course, respectively. Dry mouth was also found to be associated with younger age [18], but this data was not confirmed by the present data. Dry mouth is also considered a prognostic factor for survival, attaining a strength recommendation of level B. (The benefits of the clinical service outweighs the potential risks. Clinicians should discuss the service with eligible patients [19]). Unfortunately, treatments are limited, and evidence on the effectiveness of measures in the treatment of dry mouth is poor [2]. The most common treatments recommended were drinking water/taking sips of fluid, gargling with bicarbonate mouthwash, using an artificial saliva spray, and using an oral fungal suspension for thrush [13]. In this study, chlorexidine, antifungal drugs, benzydamine, and natural agents have been prevalently prescribed by oncologist, in most cases unsuccessfully, and generally to treat also mucositis. Thus, dry mouth is a significant problem in advanced cancer patients and should be included in the research agenda.

Dysphagia

The prevalence of dysphagia was relatively lower in comparison with other oral symptoms. However, when addressed, dysphagia may have a relevant burden for advanced cancer patients and is often associated to a short survival [19]. Head and neck cancer is a relevant risk factor, as well as a low Karnofsky level, possibly as an expression of generalized weakness. The presence and severity of dysphagia

compromised ingestion of fluid and liquids in a large number of patients, and half of these patients required alternative routes of drug administration. In subgroup analyses of head and neck cancer patients, other than tumor location, disease stage, and performance status, the presence of dysphagia altered the profile of individual symptoms that predict intake [6]. In a palliative care population, dysphagia was not mentioned among the most frequent symptoms [15, 16, 18], and in a large survey on initial referral to a palliative care clinic, males have been reported to present more frequently dysphagia [20]. This data was not confirmed in this study, as this symptom was equally distributed for gender. In advanced cancer patients followed at home, dysphagia progressively increased in frequency and intensity [21]. In a sample of patients admitted to a palliative care unit, dysphagia did not show improvement, as the symptom tended to be persistent or worsening in intensity, as fatigue, weakness, nausea/vomiting, taste alteration, diarrhea, dry mouth, and night sweats [17]. At the end of life, swallowing problems can be as high as 79 %, and these difficulties may not only result in discomfort for patients but also can raise concern for caregivers [4]. Dysphagia of liquids, decreased level of consciousness, and poor performance status appeared at high frequency with a positive likelihood ratio for impending death [22]. Similarly, dysphagia had prognostic significance for 1–2-week survival [23, 24]. Thus, dysphagia is a relevant problem in advanced cancer patients which is consistent with the progressive deterioration of patients, as an expression of debility and general weakness.

Existing studies suggest that oral symptoms are often interdependent. Dry mouth has been found to be associated with lesions of oral mucosa [25]. Dry mouth and dysphagia showed a similar trend (persistency and worsening), without showing any improvement after admission to a palliative care unit [17]. The mitigation of dysphagia in lung cancer patients treated with concurrent CT/RT was found after treating mucositis with palifermin [3].

Conclusion

In advanced cancer patients, a range of oral problems significantly may impact on the physical, social, and psychological well-being of advanced cancer patients to varying degrees. These symptoms should be carefully assessed early but become imperative in the palliative care setting when they produce relevant consequences that may be life-threatening other than limiting the daily activities, particularly eating and drinking. There is evidence to support raising the clinical focus and priority of oral care for advanced cancer patients in all settings. A better understanding of the impact of oral discomfort among advanced cancer patients is a significant care issue for hospice and palliative care teams, especially nursing staff. These problems are often underestimated, as patients often report a lack of oral assessment and virtually no input from dental experts to assist with palliating oral problems [26]. Patients tended to underreport oral symptoms, and physicians tend to address such complaints inadequately. Of interest, less than one third of the patients remembered having received information about oral sequelae associated with chemotherapy [7]. Further research of these significant issues is required.

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1. Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
2. Drafting the article or revising it critically for important intellectual content;
3. Approval of the version to be published and all subsequent versions.

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References

1. Plemons JM, Al-Hashimi I, Marek CL, American Dental Association Council on Scientific Affairs (2014) Managing xerostomia and salivary gland hypofunction: executive summary of a report from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 145:867–873
2. Hanchanale S, Adkinson L, Daniel S, Fleming M, Oxberry SG (2015) Systematic literature review: xerostomia in advanced cancer patients. Support Care Cancer 23:881–888
3. Vadhan-Raj S, Goldberg JD, Perales MA, Berger DP, van den Brink MR (2013) Clinical applications of palifermin: amelioration of oral mucositis and other potential indications. J Cell Mol Med 17:1371–1384
4. Bogaardt H, Veerbeek L, Kelly K et al (2015) Swallowing problems at the end of the palliative phase: incidence and severity in 164 unsedated patients. Dysphagia. In press
5. Lalla RV, Ashbury FD (2013) The MASCC/ISOO mucositis guidelines: dissemination amd clinical impact. Support Care Cancer 21: 3161–3163
6. Farhangfar A, Makarewicz M, Ghosh S et al (2014) Nutrition impact symptoms in a population cohort of head and neck cancer patients: multivariate regression analysis of symptoms on oral intake, weight loss and survival. Oral Oncol 50:877–883
7. Wilberg P, Hjermstad MJ, Ottesen S, Herlofson BB (2014) Chemotherapy-associated oral sequelae in patients with cancers outside the head and neck region. J Pain Symptom Manag 48: 1060–1069
8. Peterman A, Cella D, Glandon G et al (2001) Mucositis in head and neck cancer: economic and quality-of-life outcomes. J Natl Cancer Inst Monogr 29:45–51
9. Elting LS, Cooksley CD, Chambers MS et al (2007) Risks, outcomes, and costs of radiation-induced otalmucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 68: 1110–1120

10. Trotti A, Bellm LA, Epstein GB et al (2003) Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 6:253–262
11. Sonis ST (2004) *Oral* mucositis in cancer therapy. J Support Oncol 2:003–008
12. Fisher DJ, Epstein JB, Yan Y, Wilkie DJ (2014) Oral health conditions affect functional and social activities of terminally ill cancer patients. Support Care Cancer 22:803–810
13. Oneschuk D, Hanson J, Bruera E (2000) A survey of mouth pain and dryness in patients with advanced cancer. Support Care Cancer 8:372–376
14. Goldstein NE, Genden E, Morrison RS (2008) Palliative care for patients with head and neck cancer: "I would like a quick return to a normal lifestyle". JAMA 2991818–25
15. Sigurdardottir KR, Haugen DF (2008) Prevalence of distressing symptoms in hospitalised patients on medical wards: a cross-sectional study. BMC Palliat Care 7:16
16. Al-Shahri MZ, Eldali AM, Al-Zahrani O (2012) Non pain symptoms of new and follow-up cancer patients attending a palliative careoutpatient clinic in Saudi Arabia. Indian J Palliat Care 18:98–102
17. Tsai JS, Wu CH, Chiu TY, Hu WY, Chen CY (2006) Symptom patterns of advanced cancer patients in a palliative care unit. Palliat Med 20:617–622
18. Morita T, Tsunoda J, Inoue S, Chihara S (1999) Contributing factors to physical symptoms in terminally-ill cancer patients. J Pain Symptom Manag 18:338–346
19. Maltoni M, Caraceni A, Brunelli C et al (2005) Steering Committee of the European Association for Palliative Care Prognostic factors in advanced cancer patients: evidence-based clinical recommendations-a study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol 23:6240–6248
20. Walsh D, Donnelly S, Rybicki L (2000) The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. Support Care Cancer 8:175–179
21. Mercadante S, Casuccio A, Fulfaro F (2000) The course of symptom frequency and intensity in advanced cancer patients followed at home. J Pain Symptom Manag 20:104–112
22. Hui D, dos Santos R, Chisholm G et al (2014) Clinical signs of impending death in cancer patients. Oncologist 19:681–687
23. Nabal M, Bescos M, Barcons M et al (2014) New symptom-based predictive tool for survival at seven and thirty days developed by palliative home care teams. J Palliat Med 17:1158–1163
24. Gwilliam B, Keeley V, Todd C (2011) Development of prognosis in palliative care study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. BMJ Aug 25: 343
25. Alt-Epping B, Nejad RK, Jung K, Gross U, Nauck F (2012) Symptoms of the oral cavity and their association with local microbiological and clinical findings—a prospective survey in palliative care. Support Care Cancer 20:531–537
26. Rohr Y, Adams J, Young L (2010) Oral discomfort in palliative care: results of an exploratory study of the experiences of terminally ill patients. Int J Palliat Nurs 16:439–444