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Skin Cancer (T Ito, Section Editor)

Symptoms of and Palliative Treatment for Unresectable Skin Cancer

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Opinion statement

The symptom prevalence in patients with advanced cancer depends on the type of primary cancer, and the palliative treatment varies according to the nature of the primary cancer. Palliative treatment for unresectable skin cancer has not been fully discussed. Patients with unresectable skin cancer sometimes show the primary lesion in the skin and metastases to the lung, skin, liver, and bone. Pain, anorexia, and dyspnea commonly occur in such patients, and bleeding, exudate, and offensive odor are characteristically observed. For the last three symptoms, surgery and radiation are effective therapeutic options, and cryotherapy, Mohs' chemosurgery, electrochemotherapy, and some topical ointments and dressing materials are also additional options. For pain due to bone metastasis, pharmacotherapy with opioid and/or non-opioid agents is the most basic treatment, and radiation and bisphosphonate therapies are other options. For dyspnea, which is an intractable and uncomfortable symptom, morphine and oxygen play a leading role in treatment. Red blood cell transfusions may be effective for some patients with dyspnea induced by anemia. Nutritional supports and pharmacotherapy are therapeutic options for anorexia. As nutritional supports, enteral nutrition is better than parenteral nutrition. There is some evidence of progestins and corticosteroids having supportive

effects for anorexia. Dermatologic oncologists should be skilled with symptom managements to maintain the quality of life in patients with unresectable skin cancer and their families.

Introduction

Skin cancer is relatively common and is roughly subdivided into non-melanoma skin cancer (NMSC) and malignant melanoma (MM). The incidence rates are quite different among countries and races [1]. For example, the incidence rate of squamous cell carcinoma (SCC) was estimated to be 387 per 100,000 person-years in 2002 in Australia, while it was estimated to be 8.9 per 100,000 person-years between 2003 and 2005 in Croatia [2]. The incidence rates of MM were 30–60 per 100,000 person-years in Australia and New Zealand but only about 2 in Japan [1, 3]. On the other hand, the incidence rate of extramammary Paget's disease (EMPD) in Asians is ten times larger than that in Westerners [4]. Thus, the incidence rates of skin cancers vary and the mortality rates are also different among countries and races.

Two representative types of NMSC, basal cell carcinoma (BCC) and SCC, rarely have a fatal prognosis. The incidence rate of MM may most affect the mortality rate of skin cancer [1]. In some countries, even in Australia and New Zealand where there are many skin cancer patients with a fatal course, however, palliative care for unresectable skin cancer has not been fully discussed. The symptom prevalence in patients with advanced cancer depends on the type of primary lesion and metastatic sites. Common symptoms in patients with advanced skin cancer are different from those in patients with cancers in other organs. Therefore, essential knowledge and techniques of palliative treatment for advanced skin cancer are necessary. In a previous study, we showed the symptom prevalence in patients with unresectable skin cancer in Japan [5••]. In this article, we first review past literature to clarify

Table 1. Metastatic sites in patients with unresected skin cancer in Shizuoka Cancer Center [5••]

	Patients (%)				
	MM (n = 150)	SCC (n = 34)	EMPD (n = 19)	AS (n = 15)	MCC (n = 5)
Lymph node	119(79.3)	27(84.4)	16(84.2)	5(33.3)	3(60.0)
Lung	102(68.0)	18(56.3)	10(52.6)	11(73.3)	0(0)
Skin	81(54.0)	27(84.4)	9(47.4)	10(66.7)	4(80.0)
Liver	82(54.7)	9(28.1)	13(68.4)	4(26.7)	3(60.0)
Bone	71(47.3)	12(37.5)	11(57.9)	4(26.7)	0(0)
Brain	57(38.0)	3(9.4)	0(0)	1(6.7)	0(0)
Peritoneum	40(26.7)	3(9.4)	3(15.8)	0(0)	1(20.0)
Adrenal gland	21(14.0)	2(6.3)	1(5.3)	0(0)	0(0)
Pleura	18(12.0)	0(0)	2(10.5)	2(13.3)	0(0)
Pancreas	19(12.7)	0(0)	0(0)	0(0)	1(20.0)
Meninges	15(10.0)	3(9.4)	0(0)	1(6.7)	0(0)
Spleen	11(7.3)	0(0)	0(0)	0(0)	0(0)
Others	53(35.3)	4(12.5)	0(0)	2(13.3)	3(60.0)

MM, malignant melanoma; *SCC*, squamous cell carcinoma; *EMPD*, extramammary Paget's disease; *AS*, angiosarcoma; *MCC*, Merkel cell carcinoma

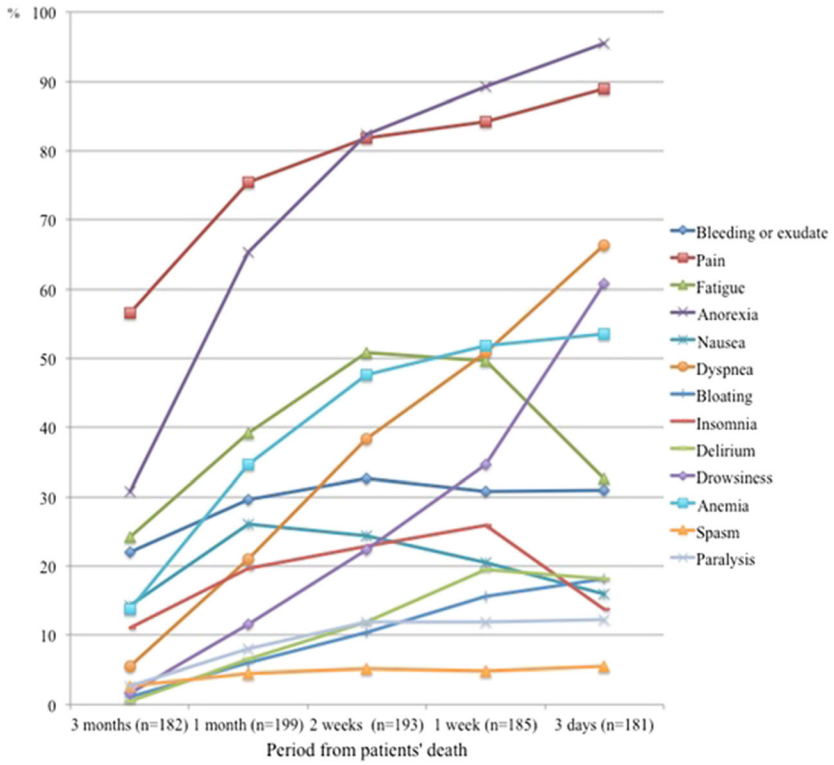

Fig. 1. Symptom prevalence in patients with unresectable skin cancer. From Goto H, Yoshikawa S, Otsuka M, Omodaka T, Yoshimi K, Yoshida Y et al. Symptom prevalence in patients with advanced skin cancer. J Dermatol. 2017;44(2):123-6. doi:https://doi.org/10.1111/1346-8138.13527, reprinted with permission from John Wiley and Sons

the characteristics of symptoms in patients with unresectable skin cancer and then we discuss the current therapeutic options for undesirable symptoms of a wide range of unresectable skin cancer including MM, SCC, EMPD, angiosarcoma (AS), and Merkel cell carcinoma (MCC).

Metastatic sites of skin cancer

It is important to identify the location of a metastatic lesion because it can have a greater influence than the primary tumor site on symptoms [6]. The common sites of metastasis vary among the types of skin cancer. The metastatic sites of five types of skin cancer (MM, SCC, EMPD, AS, and MCC) are shown in Table 1 [5••]. All types have frequent cutaneous and lymphatic lesions. The lung, liver, brain, and bone are common site of metastases from MM, EMPD, and SCC. AS has a predilection for the lung, while MCC tends to prefer to the liver. Previous studies also showed that the common sites of metastasis in patients with MM were lymph nodes followed by the skin, lung, central nervous system, and liver [7, 8]. Broughan et al. reported that 87% of cases of cutaneous SCC with metastasis had regional lymph nodes metastasis, and other patients had in-transit metastasis and distant skin metastasis [9]. Metastatic EMPD is rare, and there have been only a few studies in which metastatic sites were investigated:

metastatic sites were shown to be the lymph nodes, bone, brain, and bone marrow [10–13]. AS is rare but often has metastasis. Ito et al. investigated 43 patients with AS in Japan and showed that the lung, liver, lymph nodes, and bone were common metastatic sites of AS [14]. MCC is also rare but has been shown to be one of the most lethal skin cancers. Kiuzmina et al. reported that the most common sites of distant metastases in patients with MCC were lymph nodes followed by the liver, lung, and subcutaneous tissue [15].

Symptom prevalence in patients with advanced skin cancer

The results of our previous study showed that the symptom prevalence of skin cancer depends on the period before the patients' death [5••]. We also showed that anorexia, pain, dyspnea, hemorrhage, and exudate were common symptoms and were closely related to the site of metastasis (Fig. 1) [5••]. There were close relationships between pain and bone or skin metastasis, dyspnea and lung metastasis, anorexia and gastrointestinal tract metastasis, and hemorrhage or exudate and skin metastasis [6, 16, 17, 18•, 19–21].

Treatments

Bleeding, exudate, and offensive odor

Bleeding, exudate, and offensive odor are relatively common symptoms for patients with unresectable skin cancer as well as for patients with breast cancer and cause discomfort for patients. The incident rate of hemorrhage and exudate in patients with unresectable skin cancer is about 30% which is higher than that in a previous study in which all types of cancer were investigated [5••, 22]. Although the skin lesion itself does not always affect the prognosis of skin cancer patients, the patient's quality of life is deteriorated by the skin lesion–related symptoms. Therefore, dermatologic oncologists should consider the importance of controlling those undesirable symptoms in order to maintain the patient's quality of life.

Surgical resection is of course the best choice for controlling bleeding, exudate, and offensive odor [16, 23]. Although resection of the skin metastatic tumor cannot always prolong the patient's prognosis, palliative surgical treatment for skin metastases can provide good local control as was shown in our study [23]. Whether or not the patient can receive surgical resection may depend on the number and size of the skin metastases and the patient's performance status. When surgical resection is difficult, radiation therapy and cryotherapy are other options for controlling cutaneous lesions [24, 25]. It was reported that 78% of MM patients and 58.1% of NMSC patients showed a response to palliative radiation therapy [24, 26]. Irradiation is the best choice for unresectable and large skin tumors in the elderly patients and in patients who have poor performance status [24]. However, this therapy is difficult for patients with dementia who cannot rest during irradiation. Cryotherapy is painful but an easy option. This therapy induces cellular injury by ice formation in tumor cells [27]. Hachisuka et al. reported the usefulness of cryotherapy in combination with hyperthermia [25]. Mohs' chemosurgery is one option for controlling bleeding, exudate, and offensive odor by necrotizing the tumor surface [28–30]. This is a technique of chemical fixation of a cutaneous tumor

with Mohs' paste consisting of zinc chloride, zinc oxide, and glycerin [30]. Mohs' chemosurgery is useful for nodular cutaneous tumors, but sometimes makes ulcer deeper according to past reports and our previously experienced cases [28–30]. Attention should be given to bleeding risk when Mohs' chemosurgery is used for cutaneous lesions on sites such as the neck and inguinal region in which there are large vessels under the lesions. Kreuter et al. reported that electrochemotherapy (ECT), a combination of chemotherapy and electrical impulses, was effective for unresectable skin cancer [16, 31]. ECT often needs general anesthesia and special equipment. However, it causes only a few adverse events due to the cytostatic agent [31]. Topical ointment and dressing material are the most basic and simple option. Santos et al. reviewed topical treatments for controlling the offensive odor of malignant wounds and reported that topical metronidazole, Mesalt® dressing, curcumin ointment, and activated carbon dressing were useful [32].

Pain

A skin lesion itself is symptomatic, and pain is also the most common symptom for patients with skin cancer [5••, 16, 17, 33, 34]. In addition, 43% of patients with unresectable skin cancer had bone metastasis, which can become one of the sources of pain [5••]. Pharmacotherapy using opioid and/or non-opioid agents is the most basic method for controlling pain [18•, 19, 35]. The agents should be used by the WHO's cancer pain ladder. For cutaneous lesions, resection is the best choice for controlling pain. Radiation therapy is also effective for alleviating pain [24, 35]. In addition, in skin cancer patients with bone metastasis, palliative radiation therapy is effective for improving pain and preventing bone fracture [18•, 35, 36]. This therapy is often used in a schedule of large daily fraction dose and short treatment time [35]. Although bisphosphonate can also play an important palliative role for preventing pain and bone fracture due to bone metastasis, it commonly induces hypocalcemia and gastrointestinal problems [18•, 19, 37]. Osteonecrosis of the jaw is an uncommon but serious complication of bisphosphonate therapy [37]. Before starting bisphosphonate treatment, patients should receive a dental examination.

Dyspnea

Dyspnea is defined as an uncomfortable awareness of breathing [38]. Primary lung cancer or lung metastasis is the most frequent cause of dyspnea. Other causes are congestive heart failure, pneumonia, pulmonary embolism, pleural effusion, anemia, chest muscle weakness, psychological distress, and abdominal wall distension due to severe ascites [19, 20, 38–40]. The lung is a common metastatic site in patients with unresectable skin cancer. Eighty-seven percent of patients with MM who died and in whom an autopsy was performed had lung metastasis [8]. In our study, almost half of the patients had dyspnea 1 week before their death [5•]. Dyspnea is common in patients with lung metastasis. However, this is a subjective symptom and does not always correlate with vital signs including tachypnea and oxygen saturation [19, 39]. Therefore, the standard method for evaluating dyspnea is to ask patients directly how they feel [19]. Treatment of dyspnea is often difficult and therapeutic options with valid evidence are limited. Oxygen therapy is effective for dyspnea in patients with hypoxia [19]. Hui et al. reported the usefulness of high-flow oxygen and bilevel

positive airway pressure for dyspnea in patients with advanced cancer [41]. However, there is no evidence of the effectiveness of oxygen therapy for dyspnea without hypoxia [19]. An air fan and cold air directed on the cheek can decrease dyspnea [42]. An opioid and benzodiazepine are other important therapeutic options for dyspnea. Among opioid therapies for dyspnea, morphine is often chosen on the basis of results of previous trials [19, 43]. Attention must be given to adverse events caused by morphine including nausea, vomiting, dry mouth, and somnolence [44]. Other opioids, including oxycodone and methadone, have not been shown to be effective for dyspnea [44]. According to the previous studies, benzodiazepines may not be effective for dyspnea [43, 44]. On the other hand, it has been reported that the combination therapy of an opioid and benzodiazepine significantly improved dyspnea compared with an opioid alone or no medication [45]. A steroid is used for treatment of dyspnea in patients with chronic obstructive pulmonary disease [43]. Although dexamethasone may also be useful for dyspnea in cancer patients, evidence is still limited [43, 46]. Occasionally, dyspnea is caused by anemia [19]. Anemia is caused by various factors including adverse events of chemotherapy, undernutrition, exhaustiveness due to cancer progression, and bleeding from the tumor. About half of the patients with unresectable skin cancer had anemia 2 weeks before their death [5••]. Continuous bleeding is one of the causes of anemia. In such patients, control of bleeding from skin lesions and red blood cell transfusions are the most effective for anemia and dyspnea.

Anorexia

Anorexia or so-called cancer anorexia-cachexia syndrome is a common symptom for patients with advanced cancer. It has been estimated that 10–20% of cancer patients died from malnutrition rather than the cancer itself [21, 47]. Anorexia is also one of the predictors of survival and affects the patient's quality of life [47–50]. Anorexia is caused by various factors including cancer treatments and systemic inflammation induced by cancer [47, 49]. About half of the patients with unresectable skin cancer showed anorexia 2 weeks before their death [5••]. Patients with liver, lung, and upper digestive cancer or metastases had a higher prevalence of anorexia [21, 51]. Treatments for anorexia include nutritional supports and pharmacologic approaches. Enteral nutrition is better than parenteral nutrition [52, 53]. Enteral nutrition has the advantage of maintaining the mucosal barrier and immunologic functions as well as a low incidence of adverse events and low cost [50, 52]. Unfortunately, parenteral nutrition showed no significant survival benefit and increased the incidences of infections and mechanical complications [50, 52, 53]. There is some evidence of progestins and corticosteroids having supportive effect for anorexia [54]. Although the appropriate dose, time to start, and duration are still unknown for pharmacological treatments, those therapeutic options should be considered for anorexia in patients with unresectable skin cancer.

Other symptoms and the role of dermatologic oncologists for patients with unresectable skin cancer

Drowsiness and delirium are often seen in patients with unresectable skin cancer who as approaching death [5••]. Morita et al. reported that only 28% of

patients with cancer could achieve complex communication 3 days before their death [55]. Drowsiness and delirium are associated with brain metastasis and high-dose opioids [55, 56]. The high rate of brain metastasis, particularly in patients with MM, may be one of the reasons for the high rates of drowsiness and delirium. In addition, the use of a high-dose opioid for controlling pain due to bone and skin metastases may be linked to drowsiness and delirium. Opioid-induced cognitive dysfunction should be minimized by opioid rotation and use of non-opioid agents [55, 57].

Patients with unresectable skin cancer and families who care for the patients suffer from various symptoms and those symptoms affect their quality of life. Dermatologic oncologists should be skilled with addressing the symptoms and selecting appropriate therapeutic options for maintaining the quality of life.

Compliance with Ethical Standards

Conflict of Interest
Hiroyuki Goto, Yoshio Kiyohara, Masahisa Shindo, and Osamu Yamamoto declare they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Leiter U, Eigentler T, Garbe C. Epidemiology of skin cancer. Adv Exp Med Biol. 2014;810:120–40.
2. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069–80. https://doi.org/10.1111/j.1365-2133.2012.10830.x.
3. Tomizuka T, Namikawa K, Higashi T. Characteristics of melanoma in Japan: a nationwide registry analysis 2011-2013. Melanoma Res. 2017;27(5):492–7. https://doi.org/10.1097/cmr.0000000000000375.
4. Ito T, Kaku-Ito Y, Furue M. The diagnosis and management of extramammary Paget's disease. Expert Rev Anticancer Ther. 2018;18(6):543–53. https://doi.org/10.1080/14737140.2018.1457955.
5. •• Goto H, Yoshikawa S, Otsuka M, Omodaka T, Yoshimi K, Yoshida Y, et al. Symptom prevalence in patients with advanced skin cancer. J Dermatol. 2017;44(2):123–6. https://doi.org/10.1111/1346-8138.13527
The first study on symptom prevalence in patients with unresectable skin cancer.
6. Morita T, Tsunoda J, Inoue S, Chihara S. Contributing factors to physical symptoms in terminally-ill cancer patients. J Pain Symptom Manag. 1999;18(5):338–46.
7. Salama AK, Rosa N, Scheri RP, Herndon JE, Tyler DS, Marcello J, et al. The effect of metastatic site and decade of diagnosis on the individual burden of metastatic melanoma: contemporary estimates of average years of life lost. Cancer Investig. 2012;30(9):637–41. https://doi.org/10.3109/07357907.2012.726387.
8. Einhorn LH, Burgess MA, Vallejos C, Bodey GP Sr, Gutterman J, Mavligit G, et al. Prognostic correlations and response to treatment in advanced metastatic malignant melanoma. Cancer Res. 1974;34(8):1995–2004.
9. Brougham ND, Dennett ER, Cameron R, Tan ST. The incidence of metastasis from cutaneous squamous cell carcinoma and the impact of its risk

factors. J Surg Oncol. 2012;106(7):811–5. https://doi.org/10.1002/jso.23155.
10. Cai Y, Sheng W, Xiang L, Wu X, Yang H. Primary extramammary Paget's disease of the vulva: the clinicopathological features and treatment outcomes in a series of 43 patients. Gynecol Oncol. 2013;129(2):412–6. https://doi.org/10.1016/j.ygyno.2013.02.029.
11. Kim IY, Yun SJ, Lee JS, Jung S, Jung TY, Moon KS, et al. Brain metastasis from extramammary Paget's disease of the scrotum. J Clin Neurosci. 2014;21(4):694–6. https://doi.org/10.1016/j.jocn.2013.05.027.
12. Jones IS, Crandon A, Sanday K. Paget's disease of the vulva: diagnosis and follow-up key to management; a retrospective study of 50 cases from Queensland. Gynecol Oncol. 2011;122(1):42–4. https://doi.org/10.1016/j.ygyno.2011.03.033.
13. Cappuccini F, Tewari K, Rogers LW, DiSaia PJ. Extramammary Paget's disease of the vulva: metastases to the bone marrow in the absence of an underlying adenocarcinoma–case report and literature review. Gynecol Oncol. 1997;66(1):146–50. https://doi.org/10.1006/gyno.1997.4735.
14. Ito T, Uchi H, Nakahara T, Tsuji G, Oda Y, Hagihara A, et al. Cutaneous angiosarcoma of the head and face: a single-center analysis of treatment outcomes in 43 patients in Japan. J Cancer Res Clin Oncol. 2016;142(6):1387–94. https://doi.org/10.1007/s00432-016-2151-2.
15. Kouzmina M, Koljonen V, Leikola J, Bohling T, Lantto E. Frequency and locations of systemic metastases in Merkel cell carcinoma by imaging. Acta Radiol Open. 2017;6(3):2058460117700449. https://doi.org/10.1177/2058460117700449.
16. Kahler KC, Egberts F, Gutzmer R. Palliative treatment of skin metastases in dermato-oncology. J Dtsch Dermatol Ges. 2013;11(11):1041–5; quiz 6. https://doi.org/10.1111/ddg.12197.
17. Gaulin C, Sebaratnam DF, Fernandez-Penas P. Quality of life in non-melanoma skin cancer. Australas J Dermatol. 2015;56(1):70–6. https://doi.org/10.1111/ajd.12205.
18.• Wordliczek J, Kotlinska-Lemieszek A, Leppert W, Woron J, Dobrogowski J, Krajnik M, et al. Pharmacotherapy of pain in cancer patients - recommendations of the Polish Association for the Study of Pain, Polish Society of Palliative Medicine, Polish Society of Oncology, Polish Society of Family Medicine, Polish Society of Anaesthesiology and Intensive Therapy and Association of Polish Surgeons. Pol Przegl Chir. 2018;90(4):55–84. https://doi.org/10.5604/01.3001.0012.2904
A recent article on pharmacotherapy for pain in cancer patients.
19. Cheung WY, Zimmermann C. Pharmacologic management of cancer-related pain, dyspnea, and nausea. Semin Oncol. 2011;38(3):450–9. https://doi.org/10.1053/j.seminoncol.2011.03.016.
20. Ripamonti C, Fulfaro F, Bruera E. Dyspnoea in patients with advanced cancer: incidence, causes and treatments. Cancer Treat Rev. 1998;24(1):69–80.
21. Pressoir M, Desne S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. Br J Cancer. 2010;102(6):966–71. https://doi.org/10.1038/sj.bjc.6605578.
22. Teunissen SC, Wesker W, Kruitwagen C, de Haes HC, Voest EE, de Graeff A. Symptom prevalence in patients with incurable cancer: a systematic review. J Pain Symptom Manag. 2007;34(1):94–104. https://doi.org/10.1016/j.jpainsymman.2006.10.015.
23. Goto H, Omodaka T, Yanagisawa H, Yoshikawa S, Yoshida Y, Yamamoto O, et al. Palliative surgical treatment for cutaneous metastatic tumor is a valid option for improvement of quality of life. J Dermatol. 2016;43(1):95–8. https://doi.org/10.1111/1346-8138.12983.
24. Barnes EA, Breen D, Culleton S, Zhang L, Kamra J, Tsao M, et al. Palliative radiotherapy for non-melanoma skin cancer. Clin Oncol (R Coll Radiol). 2010;22(10):844–9. https://doi.org/10.1016/j.clon.2010.07.014.
25. Hachisuka J, Doi K, Furue M. Combination cryosurgery with hyperthermia in the management of skin metastasis from breast cancer: a case report. Int J Surg Case Rep. 2012;3(2):68–9. https://doi.org/10.1016/j.ijscr.2011.10.016.
26. Johanson CR, Harwood AR, Cummings BJ, Quirt I. 0-7-21 radiotherapy in nodular melanoma. Cancer. 1983;51(2):226–32.
27. Dawber R. Cryosurgery: unapproved uses, dosages, or indications. Clin Dermatol. 2002;20(5):563–70.
28. Uno H, Sasaki M, Osamura K, Ohtoshi S, Nakada T, Iijima M. Angiosarcoma (Stewart-Treves syndrome): palliative role of Mohs' ointment. J Dermatol. 2010;37(9):852–3. https://doi.org/10.1111/j.1346-8138.2010.00898.x.
29. Omigawa C, Hashimoto T, Hanafusa T, Namiki T, Igawa K, Yokozeki H. Modified method for applying Mohs' paste. J Dermatol. 2017;44(12):e353–e4. https://doi.org/10.1111/1346-8138.14030.
30. Nakai N, Okuzawa Y, Katoh N. Clinical usefulness of Mohs' chemosurgery for palliative purposes in patients with cutaneous squamous cell carcinoma with risk factors or without indication for surgery: three case reports. J Dermatol. 2015;42(4):405–7. https://doi.org/10.1111/1346-8138.12767.
31. Kreuter A, van Eijk T, Lehmann P, Fischer M, Horn T, Assaf C, et al. Electrochemotherapy in advanced skin tumors and cutaneous metastases - a retrospective multicenter analysis. J Dtsch Dermatol Ges.

2015;13(4):308–15. https://doi.org/10.1111/ddg.12583.
32. da Costa Santos CM, de Mattos Pimenta CA, Nobre MR. A systematic review of topical treatments to control the odor of malignant fungating wounds. J Pain Symptom Manag. 2010;39(6):1065–76. https://doi.org/10.1016/j.jpainsymman.2009.11.319.
33. Yosipovitch G, Mills KC, Nattkemper LA, Feneran A, Tey HL, Lowenthal BM, et al. Association of pain and itch with depth of invasion and inflammatory cell constitution in skin cancer: results of a large clinicopathologic study. JAMA Dermatol. 2014;150(11):1160–6. https://doi.org/10.1001/jamadermatol.2014.895.
34. Ventafridda V, Ripamonti C, De Conno F, Tamburini M, Cassileth BR. Symptom prevalence and control during cancer patients' last days of life. J Palliat Care. 1990;6(3):7–11.
35. Gough N, Miah AB, Linch M. Nonsurgical oncological management of cancer pain. Curr Opin Support Palliat Care. 2014;8(2):102–11. https://doi.org/10.1097/spc.0000000000000043.
36. Zeng L, Chow E, Bedard G, Zhang L, Fairchild A, Vassiliou V, et al. Quality of life after palliative radiation therapy for patients with painful bone metastases: results of an international study validating the EORTC QLQ-BM22. Int J Radiat Oncol Biol Phys. 2012;84(3):e337–42. https://doi.org/10.1016/j.ijrobp.2012.05.028.
37. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol. 2008;19(3):420–32. https://doi.org/10.1093/annonc/mdm442.
38. Ripamonti C, Bruera E. Dyspnea: pathophysiology and assessment. J Pain Symptom Manag. 1997;13(4):220–32.
39. Hui D, Morgado M, Vidal M, Withers L, Nguyen Q, Chisholm G, et al. Dyspnea in hospitalized advanced cancer patients: subjective and physiologic correlates. J Palliat Med. 2013;16(3):274–80. https://doi.org/10.1089/jpm.2012.0364.
40. Guirimand F, Sahut d'izarn M, Laporte L, Francillard M, Richard JF, Aegerter P. Sequential occurrence of dyspnea at the end of life in palliative care, according to the underlying cancer. Cancer Med. 2015;4(4):532–9. https://doi.org/10.1002/cam4.419.
41. Hui D, Morgado M, Chisholm G, Withers L, Nguyen Q, Finch C, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. J Pain Symptom Manag. 2013;46(4):463–73. https://doi.org/10.1016/j.jpainsymman.2012.10.284.
42. Schwartzstein RM, Lahive K, Pope A, Weinberger SE, Weiss JW. Cold facial stimulation reduces breathlessness induced in normal subjects. Am Rev Respir Dis. 1987;136(1):58–61. https://doi.org/10.1164/ajrccm/136.1.58.
43. Strieder M, Pecherstorfer M, Kreye G. Symptomatic treatment of dyspnea in advanced cancer patients: a narrative review of the current literature. Wien Med Wochenschr. 2018;168(13–14):333–43. https://doi.org/10.1007/s10354-017-0600-4.
44. Vargas-Bermudez A, Cardenal F, Porta-Sales J. Opioids for the management of dyspnea in cancer patients: evidence of the last 15 years–a systematic review. J Pain Palliat Care Pharmacother. 2015;29(4):341–52. https://doi.org/10.3109/15360288.2015.1082005.
45. Gomutbutra P, O'Riordan DL, Pantilat SZ. Management of moderate-to-severe dyspnea in hospitalized patients receiving palliative care. J Pain Symptom Manag. 2013;45(5):885–91. https://doi.org/10.1016/j.jpainsymman.2012.05.004.
46. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. J Clin Oncol. 2013;31(25):3076–82. https://doi.org/10.1200/jco.2012.44.4661.
47. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11–48. https://doi.org/10.1016/j.clnu.2016.07.015.
48. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med. 1980;69(4):491–7.
49. Del Fabbro E. Current and future care of patients with the cancer anorexia-cachexia syndrome. Am Soc Clin Oncol Educ Book. 2015;35:e229–37. https://doi.org/10.14694/EdBook_AM.2015.35.e229.
50. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. CA Cancer J Clin. 2002;52(2):72–91.
51. Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the National Cancer Center in Korea. Nutrition. 2010;26(3):263–8. https://doi.org/10.1016/j.nut.2009.04.013.
52. Nicolini A, Ferrari P, Masoni MC, Fini M, Pagani S, Giampietro O, et al. Malnutrition, anorexia and cachexia in cancer patients: a mini-review on pathogenesis and treatment. Biomed Pharmacother. 2013;67(8):807–17. https://doi.org/10.1016/j.biopha.2013.08.005.
53. Muliawati Y, Haroen H, Rotty LW. Cancer anorexia - cachexia syndrome. Acta Med Indones. 2012;44(2):154–62.
54. Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated

anorexia and weight loss. J Clin Oncol. 2005;23(33):8500–11. https://doi.org/10.1200/jco.2005.01.8010.

55. Morita T, Tei Y, Inoue S. Impaired communication capacity and agitated delirium in the final week of terminally ill cancer patients: prevalence and identification of research focus. J Pain Symptom Manag. 2003;26(3):827–34.

56. Plonk WM Jr, Arnold RM. Terminal care: the last weeks of life. J Palliat Med. 2005;8(5):1042–54. https://doi.org/10.1089/jpm.2005.8.1042.

57. Cherny N, Ripamonti C, Pereira J, Davis C, Fallon M, McQuay H, et al. Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol. 2001;19(9):2542–54. https://doi.org/10.1200/jco.2001.19.9.2542.

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