Received: 8 March 2021 | Accepted: 22 March 2021

DOI: 10.1111/1346-8138.15889

THE JOURNAL OF DERMATOLOGY

GUIDELINE

Japanese Dermatological Association Guidelines: Outlines of Guidelines for Cutaneous Squamous Cell Carcinoma 2020

Shin-ichi Ansai[1] | Yoshihiro Umebayashi[2] | Noriyuki Katsumata[3] | Hiroshi Kato[4] | Takafumi Kadono[5] | Toshihiro Takai[6] | Takeshi Namiki[7] | Masahiro Nakagawa[8] | Toshinori Soejima[9] | Hiroshi Koga[10] | Makoto Sugaya[11] | The Squamous Cell Carcinoma Guidelines Committee of the Japanese Skin Cancer Society

[1]Division of Dermatology and Dermatopathology, Nippon Medical School Musashi Kosugi-Hospital, Kawasaki, Japan

[2]Department of Dermatology, Tokyo Medical University Hachioji Medical Center, Hachioji, Japan

[3]Department of Medical Oncology, Nippon Medical School Musashi Kosugi-Hospital, Kawasaki, Japan

[4]Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[5]Department of Dermatology, St. Marianna University School of Medicine, Kawasaki, Japan

[6]Department of Dermatology, Hyogo Cancer Center, Akashi, Japan

[7]Department of Dermatology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

[8]Department of Plastic and Reconstructive Surgery, Shizuoka Prefectural Cancer Center, Nagaizumi, Japan

[9]Department of Radiation Oncology, Kobe Proton Center, Kobe, Japan

[10]Department of Dermatology, Shinshu University, Matsumoto, Japan

[11]Department of Dermatology, International University of Health and Welfare, Narita, Japan

Correspondence
Shin-ichi Ansai, Division of Dermatology and Dermatopathology, Nippon Medical School Musashi Kosugi-Hospital, 1-396 Kosugi-cho, Nakahara-ku, Kawasaki-shi, Kanagawa 211-8533, Japan.
Email: shin8113@nms.ac.jp

Abstract

In consideration of the development of treatment options for squamous cell carcinoma (SCC), the Japanese Skin Cancer Society issued the first guidelines of SCC in 2007 and revised them in 2015. Here, we report the English version of the 2020 edition of the Japanese SCC guidelines. The first half of this article is an overview of SCC including actinic keratosis and Bowen's disease, and the second half discusses three clinical questions: (i) treatment of actinic keratosis; (ii) determination of the resection margin of the primary lesion; and (iii) treatment of radically incurable cases, as contemporary problems encountered in treating SCC. In these evaluations, all processes were implemented according to the Grading of Recommendations, Assessment, Development, Evaluation system. Also, items of recommendation concerning each clinical question were determined by a multidisciplinary expert panel consisting of dermatologists, plastic/reconstructive surgeons, radiologists, and oncologists through a comprehensive literature search and systematic reviews.

KEYWORDS
actinic keratosis, bowen disease, guidline, solar keratosis, squamous cell carcinoma

This is the secondary English version of the original Japanese manuscript for Japanese Dermatological Association "Guidelines: Outlines of Guidelines for Cutaneous Squamous Cell Carcinoma 2020" (*Jpn J Dermatol* 130(12):2501–2533, 2020).

INTRODUCTION

The first Japanese Cutaneous Squamous Cell Carcinoma Guidelines were published in November 2007 as "Japanese Cutaneous Squamous Cell Carcinoma Guidelines" targeting four cutaneous malignancies: melanoma, squamous cell carcinoma (SCC), extramammary Paget's disease, and basal cell carcinoma (BCC). They were revised and published as the second edition in January 2015 (Japanese edition only). New knowledge is accumulated concerning SCC similarly to other diseases, and revision of the guidelines every few years is considered necessary to have them reflect the clinical realities. This time, approximately 5 year after the appearance of the second edition, the third edition was to be issued in 2020, and efforts were made to prepare systematized guidelines by sufficiently evaluating the literature from many sources concerning SCC by related scientific societies and the revision committee consisting of leading authorities of each field commissioned by the Japanese Dermatological Association. In the present guidelines, the epidemiology, clinical approaches, pathology, and treatments concerning SCC in general including SCC *in situ* are discussed first, followed by three clinical questions (CQs) and recommendation items derived by the GRADE approach.

In this article, the Japanese Guidelines for Cutaneous Squamous Cell Carcinoma are outlined.

LITERATURE SEARCH

Prior to a literature search, three clinical questions (CQs) were determined by the members of the Japanese Cutaneous Squamous Cell Carcinoma Guidelines Committee (expert panel), considering both the recent evolutions in clinical practice for managing cutaneous SCC and the contents of the previous version of the Japanese Cutaneous Squamous Cell Carcinoma Guidelines and other countries' guidelines. A systematic, comprehensive literature search was performed in the PubMed, Cochrane Library, and Japan Medical Abstracts Society databases with support from Dr Shinichi Abe of the Academic Information Center of the Jikei University School of Medicine and specialists from the Japan Medical Library Association. Studies published in the English language, including meta-analyses and randomized trials from January 1, 1963, to December 31, 2018, were mainly collected using relevant keywords. However, several reports that did not meet these criteria were also adopted regardless of their publication date, including non-randomized trials, retrospective studies, cases series abstracts, data presented at major international meetings, and studies reported in the Japanese language, when the committee members ruled that they should be included to determine recommendations for CQs owing to their great influence on clinical practice.

PROCESS OF GUIDELINES DEVELOPMENT

The Japanese Cutaneous Squamous Cell Carcinoma Guidelines Committee members consisted of 11 experts, including dermatologists, a plastic and reconstructive surgeon, a medical oncologist, and a radiation oncologist. After creating the CQs, evidence related to each CQ was collected using relevant keywords. The collected studies were systematically reviewed, and the strength of evidence (Table 1) was discussed by the systematic review team for each CQ. Considering the strength of evidence and other factors (e.g., risk–benefit balance and social values), the final recommendation was determined by majority vote in the expert panel meeting. In these guidelines, we established two recommendation levels (1 = strong or 2 = weak) in two directions ("do it" or "do not do it") (Table 2). A recommendation was accepted if more than 50% of the expert panel members reached an agreement with pursuing either direction and the vote for the opposite direction was less than 20%. Furthermore, if 70% of the expert panel members suggested the evidence was strong, then a strong recommendation was established. Otherwise, all recommendations were set as "weak". As the policy of the Japanese Squamous Cell Carcinoma Guidelines Committee, voting for the recommendations included as many expert panel members as possible, but those members who disclosed academic or financial conflicts of interest regarding each CQ restrained from the voting for the CQ. The whole process of drafting the guidelines was performed according to the GRADE system.

TABLE 1 Level of evidence according to the GRADE scheme

Level	Strength of evidence	Definition
A	High	High confidence in the correlation between the true and estimated effect
B	Moderate	Moderate confidence in the estimated effect; it is possible that the true effect is very different from the estimated effect
C	Low	Limited confidence in the estimated effect; the true effect may be very different from the estimated effect
D	Very low	Very little confidence in the estimated effect; the true effect is very likely different from the estimated effect

TABLE 2 Strength of recommendation

Recommendation level	Direction	Description
1 (strong) for	Do it (i.e., recommend doing)	A judgment that most well-informed people would make
2 (weak) for	Probably do it (i.e., suggest doing)	A judgment that a majority of well-informed people would make but a substantial minority would not
2 (weak) against	Probably not do it (i.e., suggest not doing)	A judgment that a majority of well-informed people would not make but a substantial minority would make
1 (strong) against	Not do it (i.e., recommend not doing)	A judgment that most well-informed people would not make

Overview of SCC

1.1.1 | Concepts and Definitions

Squamous cell carcinoma is a malignant neoplasm differentiating into stratified squamous epithelium (i.e., epidermal keratinocytes).

Squamous cell carcinoma is characterized by differentiation into keratinocytes and shows intercellular bridge formation,[1] keratinization,[1,2] sheet-like proliferation,[1] and keratin expression.[2]

Squamous cell carcinoma remaining in the epidermis is called SCC *in situ*. Typical SCC *in situ* are Bowen's disease and actinic keratosis (solar keratosis). Actinic keratosis may be excluded from SCC *in situ* and be regarded as a precancerous lesion[3] or carcinoma precursor.[4]

1.1.2 | Epidemiology

In Japan, SCC is the commonest cutaneous malignancy next only to BCC and is increasing with aging of the population. Although there are no clear statistics concerning the incidence of SCC in Japan, 2507 cases were reported during the 5 years from 1987 to 1991. The incidence is reported to be approximately 2.5/100 000 persons annually,[5] and it is estimated to be approximately 1.5–2-times higher than the incidence of malignant melanoma.[6,7] Also, according to a survey of approximately 100 facilities from 1987 to 2001, SCC accounted for 28% of the 29 170 cases of SCC, BCC, and malignant melanoma combined. In this survey, also, there were 8975 cases of solar keratosis.[8]

In a survey conducted in 2008 in approximately 180 facilities in Japan, there were 1050 cases of SCC and 741 cases of Bowen's disease.[9] Also, in a survey conducted in 2011 in approximately 200 facilities in Japan, there were 1247 cases of SCC and 874 cases of Bowen's disease.[10] Approximately 80% of the patients with SCC were aged 70 years or above at the time of examination, were most frequently in their 80s, and their mean age was 77.8 years. The male : female ratio was 1.15:1 with males occupying a slight majority. SCC developed most frequently from solar keratosis in 251 cases (23.9%), from Bowen's disease in 68 (6.4%), and from burn scar in 42 (4.0%).[8] Concerning the site, SCC occurred in the head and neck region in 51.0%, trunk in 9.6%, upper extremity in 8.7%, lower extremity in 16.9%, with the head and neck lesions accounting for the majority. Reliable data indicating a relationship between SCC and ultraviolet light are scarce concerning the Japanese population, but the occurrence of SCC in areas exposed to sunlight in approximately 60% of the patients suggests an involvement of ultraviolet light, although not as conspicuously as in white people.[11]

Regarding Bowen's disease, the mean age of the patients at the examination was 75.2 years, the patients were most frequently in their 70s, and the male : female ratio was 1:1.21 with females occupying a slight majority contrary to the male : female ratio of SCC patients. In addition, the lesions of Bowen's disease were solitary in 678 cases but multiple in 59 (7.9%). Also, it affected the lower extremity in 38.3%, trunk in 26.2%, and upper extremity in 18.2%.[9]

The incidence of solar keratosis is estimated to be 100–120/year per 100 000 people in Japan, and this means that 100 000 or more people in Japan develop solar keratosis annually.[12]

As for the number of SCC patients overseas, more than 69 000 patients with non-melanoma cutaneous cancer were registered in 2007 in the UK (population: 65 million), and the annual number of cases is estimated to exceed 100 000.[13] SCC is also increasing in the USA (population: 327 million), and 9–14% of men and 4–9% of women are considered to develop the disease during their lifetime.[14] There is also a report that one of every four people suffer skin cancer by the age of 70 years,[15] and ultraviolet light is considered responsible in 90% of these cases.[16] According to the Medicare data in the USA, the incidence of non-melanoma cutaneous malignancies per 100 000 people was 6075 in 2006 but increased to 7320 in 2012.[17] However, it must be noted that this figure includes patients with BCC and carcinoma *in situ* and a considerable number of those with solar keratosis. Also, according to the data in 2012, 3278 of 100 000 people were treated for SCC including carcinoma *in situ*.[17] Therefore, in the USA, more than 1 million people are diagnosed with SCC including SCC *in situ* annually with more than 15 000 deaths.[18] Another report estimated that the number of newly diagnosed cases of SCC is 180 000–520 000 annually with 3932–8791 deaths.[19] By race, the incidence of SCC per 100 000 people is estimated to be 7–360/year in whites, 2.6–2.9/year in Asians, and 3/year in blacks.[20] In addition, solar keratosis, which is a precursor lesion of SCC, is the most frequent precancerous

lesion estimated to be affecting more than 40 million people in the USA.[21]

1.1.3 | Tissue of origin, pathogenic factors, and prevention

Squamous cell carcinoma often develops from prodromal conditions and intraepidermal cancer. Prodromal conditions include burn scar, chronic radiation dermatitis, suppurative hidradenitis, chronic discoid lupus erythematosus, and decubitus ulcer, and intraepidermal cancers include solar keratosis, Bowen's disease, porokeratosis, and bowenoid papulosis of the external genitals. Saida *et al*. classified prodromal conditions of SCC of the skin into three groups. Group 1 is conditions in which scarring or chronic inflammation persists for a long time such as burn scar and chronic radiation dermatitis; Group 2 is SCC *in situ* or its early lesions such as Bowen's disease and solar keratosis; and group 3 is systemic disorders or conditions from which SCC of the skin often develops such as xeroderma pigmentosum and chronic arsenic poisoning.[22] Accurate determination of the tissue of origin is considered important as it relates to the subsequent diagnosis and therapeutic approach.

Pathogenic factors can be classified into external and host factors. Typical external factors are ultraviolet light, radiation, and chemicals, and ultraviolet light in sunlight, in particular, is considered to be involved in carcinogenesis as it directly damages DNA and causes mutations. When exposed to ultraviolet light, pyrimidine dimers are generated in DNA, and the damage is repaired by the DNA repair mechanisms including nucleotide excision repair.[23] However, if more lesions than can be repaired have been caused in DNA, their repair becomes insufficient, and pyrimidine dimers are considered to persist. This is considered to cause gradual accumulation of many mutations, which leads to carcinogenesis. Chronic inflammation is also considered to be involved in carcinogenesis by increasing oxidative stress as it also directly damages DNA.[24]

Host factors include genetic diseases, such as xeroderma pigmentosum, porokeratosis, and epidermodysplasia verruciformis, and immunodeficiency due to treatment for other diseases, such as organ transplantation, is also considered to be a possible factor. In xeroderma pigmentosum, functional defects are caused by genetic abnormalities of DNA damage repair systems such as nucleotide excision repair.[25] The resultant insufficiency of repair of DNA lesions is considered to lead to carcinogenesis. Also, in an immunodeficient state, analysis of patients with post-transplantation skin tumors indicated that transplantation recipients have a 65-fold increase in the risk of developing skin tumors and that immunosuppression caused by immunosuppressants administrated to transplantation recipients increases the occurrence of cutaneous SCC.[26]

For the prevention of SCC, resection of intraepidermal cancer, which serves as the tissue of origin, appropriate treatment, and control of exposure to ultraviolet light, which is an external factor, such as avoiding massive exposure to sunlight are recommended.

1.1.4 | Clinical features

Squamous cell carcinoma occurs frequently in areas exposed to sunlight, such as the face, forehead, scalp, ear, and dorsum of the hand of elderly people, but can also affect other areas and the mucocutaneous junction.[27,28]

Generally, SCC occur as slightly elevated reddish or normal skin-colored plaques or nodules with hyperkeratotic surface. However, they may show an eroded surface, be ulcerated and crusted or necrosed, or present with a cauliflower-like appearance.[29]

Actinic keratosis occurs frequently in light-exposed areas of elderly people,[30] primarily show telangiectasia and a slightly scaly surface in an early stage but often develops into erythematous plaques accompanied by keratotic scales on the surface.[31] There are also other types, such as those that present with clinical features called cutaneous horn characterized by thick cornification and horny elevations, that show milder cornification and epidermal thickening, and that are brownish or blackish in color due to melanin accumulation (pigmented actinic keratosis). Palpation of infiltration, and inflammation and bleeding, are signs suggestive of transition to invasive SCC.[31]

Bowen's disease frequently affects the head and neck region and the ears of males and the lower extremities of females and enlarges gradually.[31] Its typical clinical picture is an irregularly shaped but relatively distinctly bordered keratotic plaque often of mixed colors such as red, normal skin color, brown, and gray.[32]

1.1.5 | Histopathological features

Squamous cell carcinoma is a tumor that arises from the epidermis or adnexal epithelium and shows irregular proliferation of tumor cells differentiating into epidermal keratinocytes with nuclear atypia.[33] SCC is classified into SCC *in situ* and invasive SCC according to the degree of progression.

Squamous cell carcinoma *in situ* and invasive SCC are differentiated from a comprehensive pathological viewpoint on the basis of whether the epithelial basement membrane is broken or not by infiltration of tumor cells. However, because this judgment is extremely difficult to make in routine hematoxylin–eosin (HE)-stained specimens, and because tumor cells are considered to occasionally infiltrate by forming the basement membrane, the distinction is actually made according to whether tumor cells have infiltrated to the reticular dermis or not.

1.5.1 | SCC in situ

1. Actinic keratosis

In actinic keratosis, tumor cells differentiating into keratinocytes with large and atypical nuclei, which are occasionally accompanied by mitoses, irregular proliferation, showing crowded nuclei, primarily in the lower epidermis. Tumor cells often proliferate like buds from

the lower margin of the epidermis. Also, fissures frequently develop between tumor cells and keratocytes in the spinous layer. The horny cell layer of the interfollicular epidermis is usually accompanied by parakeratosis and is stained eosinophilically. Parakeratosis is often not observed in the epithelium of the hair follicle infundibular region, which is stained basophilically. In this stage, eosinophilic and basophilic areas appear alternately in the horny layer. This is the pink and blue sign. Tumor cells often infiltrate primarily along the basal layer of the hair follicle and sweat duct epithelium. As the lesion progresses, tumor cells begin to occupy the full thickness of the epidermis similarly to Bowen's disease. Such a lesion is called the bowenoid type. Even in this state, ordinary actinic keratosis is often observed in some parts of the lesion. If parakeratosis or bud-like growth is inconspicuous, it is difficult to histopathologically diagnose actinic keratosis even though large nuclei, nuclear atypicality, or an irregular arrangement are noted in keratinocytes of the lower epidermis. Still, it is possible to diagnose early lesions of actinic keratosis based on the clinical findings of actinic keratosis. If wart or cutaneous horn formation is clinically observed, there may be an overall histopathological structure resembling that of warts. Solar elastosis in the dermis is a nearly essential condition for a pathological diagnosis of actinic keratosis.

2. Bowen's disease

In Bowen's disease, tumor cells differentiate into keratinocytes with large atypical nuclei proliferate diffusely and irregularly in all layers or part of the epidermis. Mitoses, many of which are atypical, are observed, and dyskeratotic cells are often noted. Clumping cells that resemble multinucleated giant cells are occasionally present. A row of keratinocytes with small uniform nuclei may remain in the lowest layer of the epidermis that is called eye-liner sign, and they are considered residual normal keratinocytes. Tumor cells often infiltrate the hair follicle epithelium or sweat ducts. There may be a verrucous or crater-like general structure. The presence or absence of solar elastosis does not matter.

3. Others

A condition that exhibits a clinical profile similar to that of condyloma acuminatum and a pathological profile similar to that of Bowen's disease is called bowenoid papulosis. SCC *in situ* arising in a scarred area is also called cicatricial keratosis, and its pathological features often resemble those of actinic keratosis. Radiation keratosis developing on chronic radiodermatitis and arsenic keratosis observed in patients with chronic arsenic poisoning are also known.

1.5.2 | Invasive SCC

1. Clinicopathological classification

Although various classification methods have been proposed,[34] the following is one based on intraepithelial lesions.[35] This system is a modification of the classification first reported by Ackerman *et al*.[36,37] It reflects the prognosis relatively well.

a. Actinic keratosis type

The type in which actinic keratosis is present as an intraepithelial lesion. It occasionally exhibits a crater-like appearance, in which case differentiation from keratoacanthoma (KA) is necessary. Such a lesion may be distinguished as crateriform SCC.

b. Bowen type

The type with Bowen's disease as an intraepithelial lesion.

c. KA type

Lesions that show change characteristic of SCC in KA. It is synonymous with KA with conventional SCC components.

d. Cystic type

Lesions arising from the wall of keratinous cysts from the dermis to the subcutaneous adipose tissue. They correspond to so-called SCC originating from epidermal cysts.

e. Genital type

Lesions occurring in the external genitals except those arising from scar or chronic radiodermatitis and those arising in xeroderma pigmentosum. Such lesions are classified as an independent category, because it is difficult to determine whether they have developed from Bowen's disease or from bowenoid papulosis, and because SCC affecting this region have a relatively poor prognosis.

f. Cicatricial type

Lesions occurring on trauma or burn scar confirmed clinically or by medical interview.

g. Radiodermatitis type

Lesions occurring on chronic radiodermatitis confirmed clinically or by medical interview.

h. Xeroderma pigmentosum type

Lesions occurring in patients diagnosed with xeroderma pigmentosum.

2. Histopathological findings

A. Histopathological findings common to invasive SCC

Tumor cells that have differentiated to keratinocytes with nuclear atypia irregularly proliferate continuously from SCC *in situ* in the epidermis or adnexal epithelium and infiltrate the reticular dermis and deeper areas. The tumor cell nest is distinctly or indistinctly bordered.

The tendency of tumor cells to keratinize can be confirmed by formation of cancer pearl, but, if they are poorly differentiated, cancer pearl is not notable, and only individual cell keratinization may be confirmed. Although keratinization of individual cells can be confirmed by eosinophilic staining of the cytoplasm, particularly, around the nucleus by HE staining, it is necessary to make clear distinction from individual cell necrosis accompanied by nuclear degeneration.

B. Typical histopathological findings in various clinicopathological disease types

a. Actinic keratosis type

Clear actinic keratosis is observed around infiltrative lesions or in the overlying epidermis. It is occasionally accompanied by acantholysis. Also, intradermal lesions may not form clear cell nests and exhibit an appearance resembling spindle cell SCC with proliferation of spindle-shaped cells.

b. Bowen type

Clear Bowen's disease is observed around infiltrative lesions or in the overlying epidermis.

c. KA type

Lesions of this type have a basic overall structure in which exophytic and endophytic proliferation is observed, there is a crater-like structure in the center of the lesion, keratin mass is contained inside, and the epidermis around the tumor is curved and turned over at the junction to the tumor (epithelial lip). There are parts of the lesion that can be clearly diagnosable as KA as mentioned below. That is to say, there are areas that show irregular proliferation of keratinocytes with nuclear atypia in part of the lesion with an area of lumpy proliferation of cells rich in eosinophilic cytoplasm with no nuclear atypicality.

d. Cystic type

Lesions in which there is irregular proliferation of keratinocytes with nuclear atypia continuous from a keratinous cyst.

e. Genital type

Squamous cell carcinoma *in situ* with Bowen's disease and bowenoid papulosis including erythroplasia of Queyrat, in which the two conditions are difficult to discriminate.

f. Cicatricial type

Clear scar is observed in or around the lesion. Intraepidermal lesions often arise from the lower layers of the epidermis and resemble actinic keratosis.

g. Radiodermatitis type

Relatively specific diagnosis of this type is possible if proliferation of fibroblasts with bizarre nuclei is observed in the lesion or the dermis around the lesion, but its differentiation from the cicatricial type is difficult if such findings are indistinct.

h. Other histopathological subtypes

The World Health Organization (WHO) classification lists the following as histopathological subtypes of SCC.[33]

1) Acantholytic SCC

Intercellular adhesion of tumor cells is histopathologically lost, resulting in a glandular structure. The prognosis was considered poorer in this type than in other types in the past[42] but not to differ according to recent reports.[38,39]

2) Spindle cell SCC

Poorly differentiated SCC that has lost the properties of squamous epithelial differentiation. Its prognosis is generally considered poorer than that of other types of SCC.[40]

3) Verrucous SCC (verrucous carcinoma)

See 7-a.

4) Adenosquamous carcinoma

This is synonymous with squamoid eccrine ductal carcinoma, which is a sweat gland tumor.

5) Clear cell SCC

Histopathologically, cells with clear cytoplasm are notable. This type is considered to have no particular difference in prognosis.[41]

6) SCC with sarcomatoid differentiation

Squamous cell carcinoma that has sarcomatous components, such as cartilage, bone, and striated muscle, as well as typical keratinization.

7) Lymphoepithelioma-like carcinoma of the skin

Squamous cell carcinoma that shows dense lymphocyte and plasma cell infiltration around small aggregates of undifferentiated tumor cells positive for AE1/AE3 or cytokeratin (CK)5/6. It resembles nasopharyngeal lymphoepithelioma-like carcinoma.

8) Pseudovascular SCC

Cytokeratin-positive tumor cells form a cord-like structure, which contains voids resembling vascular lumens. Although it resembles angiosarcoma, tumor cells are negative for vascular endothelial markers. It is a highly malignant SCC. The stroma often shows marked retention of mucin (mucus).

9) SCC with osteoclast-like giant cell

Highly malignant SCC in which inflammatory cell infiltration is observed around aggregates of intermediately or poorly differentiated tumor cells, which are mixed with non-tumorous osteoclast-like cells.

C. Immunohistochemical findings[33,42]

Cytokeratin 1 and CK10 are often positive. AE1/AE3 and CK5/6 are also positive in most cases. CK19 is often positive, but CK7 is negative except in only a few cases. Epithelial membrane antigen (EMA) is also positive in many cases. Ber-EP4 is basically negative[43] but is positive in rare cases.

1.1.6 | Imaging diagnosis

1.6.1 | Imaging studies before surgery

There has been no study with a high evidence level that investigated preoperative imaging findings, recurrence rate, and survival rate in SCC patients. In the National Comprehensive Cancer Network (NCCN) Guidelines,[44] imaging examinations to be performed before surgery of local lesions, regional lymph nodes, and distant metastasis are described. Concerning local lesions, magnetic resonance imaging (MRI) is recommended for those suspected to have tumor infiltration to bones and deep soft tissues and those suspected to have tumor infiltration to nerves and lymphatic vessels, and CT examination is considered useful for those suspected to have bone infiltration. Regarding imaging studies of reginal lymph nodes, the guidelines recommend fine-needle aspiration cytology for those with enlargement observed clinically or suggested by imaging examinations. If fine-needle aspiration cytology is positive, contrast-enhanced CT of reginal lymph nodes, positron emission tomography (PET)/CT examinations, and imaging examinations of the thoracic, abdominal, and pelvic regions except lymph nodes are recommended. The European Organization for Research and Treatment of Cancer (EORTC) Guidelines[45] recommend ultrasonography of lymph nodes to detect lymph node metastasis. Ultrasonography is reported to be essential particularly when the thickness of the tumor is expected to exceed 6 mm. However, whether imaging examinations in patients with no physical lymph node enlargement improve the outcome is presently unclear.

Barzilai *et al*.[43] performed a case series study in 22 head and neck SCC patients and reported histological metastasis to the parotid gland in 68% and metastasis to cervical lymph nodes in 45.5%. Imaging examinations failed to diagnose 36% of the metastases to the parotid gland and 20% of the metastases to the cervical lymph nodes. They also reported that while the 5-year survival rate was 60% in patients with parotid gland metastasis alone and 100% in those with cervical lymph node metastasis alone, it was 0% in those with metastases to both. Parotid and neighboring lymph nodes are important as sites to which SCC metastasizes first, and imaging examinations of the head and neck region in patients predisposed to lymph node metastasis is useful for the determination of the extent of surgery and the appropriateness of postoperative radiation therapy. Nemzek *et al*. performed a case series study in 19 head and neck cancer patients (including 10 with SCC). The sensitivity of MRI was 95% for detecting perineural infiltration. However, the sensitivity was reported to be 63% concerning accurate evaluation of the extent of perineural infiltration. In determining the extent of resection, resection must be designed by referring to the results of MRI along with the results of other examinations.[46] Sharma *et al*.[47] compared postoperative pathological findings and preoperative CT findings in 30 patients who underwent surgery for lymph node metastasis and reported the usefulness of preoperative CT examination by detecting central necrosis in preoperative CT images in 19 of the 30 patients. Concerning preoperative PET/CT examination, there have been case series studies, but no data concerning the prognoses are available, and, from the viewpoint of cost–performance, it is considered necessary to perform the examination in selected rather than all patients.[48,49] As observed above, it is not necessary to perform imaging examinations in all SCC patients, and priority should be placed on careful history-taking and physical examination.

Sentinel lymph node biopsy is covered by health insurance when the lesion exceeds 2 cm in length in Japan. Therefore, it is necessary to accurately determine the tumor size. If the measurement of the tumor size and judgment of whether the lesion is *in situ* or not are difficult by physical examination alone, examinations, such as high-frequency ultrasonography of the tumor itself, are recommended. Palpation is performed first for the examination of the presence or absence of lymph node metastasis, but if the judgment by palpation is difficult due to scar or chronic skin ulcer, modalities, such as ultrasonography and CT, are employed. Also, as the presence or absence of perineural infiltration is related to the recurrence, it must be detected before surgery, and the knowledge is useful for the evaluation of the indication for postoperative adjuvant therapies.[50] Exploration for distant metastases is necessary for the evaluation of indications for radical surgery of regional lymph nodes in patients already confirmed to have regional lymph node metastasis, but how much it contributes to the improvement in the outcome is unknown. Since the occurrence of distant metastasis is very rare in SCC patients without lymph node metastasis, it is unnecessary to perform imaging examinations as a routine for exploration of distant metastases except when it is clinically suspected.

1.6.2 | After treatment

Although there have been no reports that convincingly showed how much imaging examinations after treatment of cutaneous SCC can

contribute to the detection of local recurrence, regional lymph node metastasis, or distant metastasis and improvements in the survival rate, careful examination of the primary focus and regional lymph nodes by inspection and palpation to check the presence or absence of recurrence and metastasis is considered important in the high-risk groups as indicated by the report that 95% of local recurrences and metastases occur within 5 years after treatment.

1.1.7 | Related diseases and diseases to be differentiated

a. Verrucous carcinoma

Verrucous carcinoma (verrucous SCC) is a well-differentiated and low-grade type of SCC that clinically shows a verrucous or cauliflower-like appearance. It proliferates locally and extends to deep areas as it progresses but metastasizes rarely. It frequently affects the lips, external genitalia, and planta, and lesions occurring in these regions are respectively called oral florid papillomatosis, giant condyloma acuminatum (Buschke–Löwenstein tumor), and epithelioma cuniculatum.[2] Papillomatosis cutis carcinoides, which often occurs in the lower leg, may be included in this category.[51,52]

Histopathologically, the lesion shows asymmetric exophytic and endophytic proliferation.[51,52] It is differentiated from usual SCC by the following points. First, the tips of the epidermal processes are rounded and bulbous (contrasting with thin and sharp tips of pseudocarcinomatous hyperplasia).[53] Second, the lesion shows expansive/pushing growth rather than infiltrative/destructive growth[51] (progresses by "bulldozing" rather than "stabbing" the surrounding tissues).[54] Third, tumor cells rarely show atypia, individual cell keratinization, or mitoses.[51,54,55] Fourth, neutrophilic abscesses are formed in the epidermis (the presence of neutrophils is an important clue to the diagnosis).[51]

b. Bowenoid papulosis of the genitalia

Bowenoid papulosis of the genitalia is multiple black papules arising in the external genitalia and presents histological findings similar to those of Bowen's disease. Human papilloma virus (HPV) is often detected. The disease tends to occur more frequently in sexually active young people and forms black papules or flat plaques 2–20 mm in diameter in the external genitalia, some of which may be verruciform. Histopathologically, thickening and misalignment of the epidermis, nuclear atypia and atypical mitoses, clumping cells, and multinucleated cells are observed similarly to Bowen's disease. Clinically, melanin deposition in the basal layer and melanophages in the upper layer of the dermis are common findings in markedly pigmented lesions. HPV can be detected frequently, and high-risk type HPV16 is detected, particularly, in typical cases. Since this disease may serve as an infection source for uterine cervix cancer, it is recommended to be completely treated by methods, such as liquid nitrogen cryocoagulation and electric cauterization, and not to be left untreated.

c. KA

The disease concept of KA is controversial, with some considering it to be benign[56,57] and others regarding it as a subtype of SCC.[58] Also, KA has been suggested to be a single entity or to be a term that generally indicates different tumors similar in architecture.[59-62]

Clinically, KA occurs frequently in the head and neck region and face of older people as crater-like nodules containing keratinous plugs in the center, and its periphery seems to be a glossy extension of the normal epidermis.

Histopathologically, the lesion has a crater-like structure with a keratinous plug in the center and shows external and internal proliferation. The neoplastic cells are characterized by rich ground glass-like mildly eosinophilic cytoplasm, so-called large pale-pink cells. The neoplastic cells may have a degree of atypicality, but if large pale-pink cells are only slightly atypical, the lesion frequently regresses spontaneously and does not follow a malignant course. On the other hand, if clearly atypical cells rather than typical large pale-pink cells are present in some parts of the lesion, it has been reported not to regress spontaneously and to have malignant potential.[61,62]

However, clinical or pathological differentiation between KA and invasive SCC is occasionally difficult even by examination of biopsy specimens that permit evaluation of the entire lesion, and many authors have recommended complete resection when KA is clinically suspected.[63]

d. BCC

The differentiation of BCC from SCC with tumor cells resembling basal cells is occasionally difficult. Also, BCC often forms collision tumors with SCC in the face. BCC can be differentiated by nuclear palisading in the periphery of the tumor cell nests and mucin accumulation around and within the tumor cell nests. Most importantly, however, while SCC forms lesions in the epithelium (epidermis or adnexal epithelium), BCC is continuous with the epithelium but does not form intraepithelial lesions. By immunohistochemical staining, neoplastic cells of BCC are Ber-EP4(+) and EMA(−), but those of SCC are Ber-EP4(−) and EMA(+).[42,64]

e. Other diseases to be differentiated

1) Porocarcinoma

Concerning porocarcinoma, lumen formation (sweat duct differentiation) by squamoid cells with nuclear atypia (cuticular cell) is an important finding. SCC may present porocarcinoma-like histological features due to acantholysis or a proliferation of tumor cells in the sweat ductal epithelium, but demonstration of sweat ductal differentiation of tumor cells is necessary for diagnosing porocarcinoma. For immunohistochemical staining, carcinoembryonic antigen (polyclonal), carbohydrate antigen 19-9, and, recently, CD117 have been reported to be useful.[65]

2) Sebaceous carcinoma

The presence of cells showing sebaceous gland differentiation is indispensable for the diagnosis of sebaceous carcinoma. By HE staining, they are recognized as cells with foamy cytoplasm and scallop shell-like nuclei. Sebaceous carcinoma with few cells showing sebaceous gland differentiation is often difficult to differentiate from SCC. Adipophilin is the most useful for immunohistochemical staining.[42]

3) Metastatic SCC of the skin

Metastatic SCC of the skin must be eventually diagnosed according to the presence or absence of the primary focus, but the presence or absence of SCC *in situ* is the most important histopathological feature of the lesion.

1.1.8 | Surgical treatments

1.8.1 | Introduction

The response rate to chemotherapy of SCC tends to be lower than that of malignant melanoma and other cutaneous malignancies. Therefore, surgery is still one of the most important treatment options along with radiation therapy. For the future, immune checkpoint inhibitors are expected to be introduced also to the treatment for SCC, and drastic change is considered to occur as in the treatment for malignant melanoma. In this section, the significance and indications of current surgical treatments are outlined.

1.8.2 | Resection of the primary focus

1) Resection margins (lateral, deep)

See CQ2 for resection margins.

2) Mohs surgery ([1]not covered by health insurance as of April 2019 in Japan)

Mohs surgery is a technique to check whether the tumor has been completely resected or not before reconstruction by intraoperative pathological examination and is one of the procedures widely used in Western countries. The surgeon resects the tumor at the point considered to be its macroscopic margin. The tissue frozen on the cryostat is sliced horizontally, a section is prepared from the lowest layer and stained. If tumor cells are observed, additional resection is made, and a tissue section is prepared again. By repeating this procedure, only the tissue in which the tumor is present can be removed. Also, resection with the minimum margin is made possible by applying the same technique to the circumferential margin of the tumor. This technique makes one-stage tumor resection with a minimum margin possible.[66]

Rowe *et al.* performed a case series study and compared the results of Mohs surgery and usual surgical resection of SCC. According to their report, the recurrence rate of primary skin lesions after a long-term follow-up for 5 years or longer was 8.1% in the surgical resection group but 3.1% in the Mohs surgery group, and the postoperative recurrence rate of lesions that had developed local recurrence was 23.3% in the usual surgery group but low at 10.0% in the Mohs surgery group. In addition, the recurrence rate in neurotropic cases of SCC was 47.2% in the usual surgical resection group but 0% in the Mohs surgery group. Moreover, in SCC with a tumor diameter of 2 cm or greater, the cure rate was 58.3% in the surgical resection group but high at 74.8% in the Mohs surgery group. Since the metastasis rate of SCC increases to 30.3% after recurrence, and the survival rate after metastasis decreases to 34.4%, the authors recommended Mohs surgery because of the low postoperative recurrence rate.[67] Furthermore, van Lee *et al.*[68] compared patients who underwent Mohs surgery and those who underwent usual surgery among 672 SCC patients. While the local recurrence rate was 8% after usual surgery, it was low at 3% after Mohs surgery, indicating the usefulness of Mohs surgery. A low recurrence rate as an advantage of Mohs surgery was also reported by Leibovitch *et al.*[69] They performed a case series study in patients who underwent Mohs surgery in 1993–2002 and were registered in the Australian Mohs surgery database (a total of 1263 patients of whom 61.1% were newly diagnosed, 38.9% were recurrent cases, and 96.5% had primary SCC of the head and neck region). As a result, in the recurrent cases, the maximum diameter ($p < 0.0001$) and postoperative defect ($p < 0.0001$) were larger, number of resections in Mohs surgery was higher ($p < 0.0001$), and the percentage of those who showed infiltration beyond the preoperative clinical margin was higher ($p = 0.02$) than in the newly diagnosed cases. In addition, the recurrence rate during the 5 years after Mohs surgery was 3.9% in all patients (2.6% in the newly diagnosed group, 5.9% in the recurrence group), and none had metastasis. Major factors related to the recurrence were a previous history of recurrence, infiltration beyond the preoperative clinical margin, and number of resections in Mohs surgery (the site of the tumor, histological type, size at the first examination, or postoperative defect was not related to the 5-year recurrence rate). Since the local recurrence rate was low after Mohs surgery although many high-risk patients were included in the subjects of this study, complete resection is suggested to be most important. As observed above, Mohs surgery has the advantage of a low recurrence rate and is considered to be more useful than usual surgical resection. However, this technique is complicated, requires special training for acquisition, and requires time and labor for implementation of a series of processes, and it has not gained wide acceptance in Japan because of these disadvantages.

1.8.3 | Resection of distant metastases

In existing reviews (Cochrane Library, Clinical Evidence: Issue 9, Evidence-based Dermatology) and English and Australian

[1]The disease stages that appear in the test are based on the Union for International Cancer Control (UICC) classification at the time of the studies and differ in many respects from those by the current staging system.

guidelines about SCC, there is no mention about resection of distant metastases. NCCN Guidelines of the USA[44] recommend participation in clinical trials of immune checkpoint inhibitors and chemotherapy, but surgery is listed with palliative radiation therapy as treatments for symptomatic sites. Therefore, surgical treatment for metastatic foci of SCC is considered to be limited to cases in which resection is easy and expected to be useful as palliative therapy.

1.8.4 | *Sentinel lymph node biopsy*

Fukushima *et al*. performed sentinel lymph node biopsy in 54 SCC patients and reported that metastases were observed in sentinel lymph nodes in four patients, all of whom had T2 lesions (≥2 cm in long diameter).[70] Based on this report, in Japan, sentinel lymph node biopsy in SCC patients is covered by health insurance when the lesion exceeds 2 cm in length. There are a few reviews concerning sentinel lymph node biopsy for SCC in Western countries. In a systematic review by Tejera-Vaquerizo *et al*.,[71] metastasis to sentinel lymph nodes was observed in 7.9% of all patients, but the survival rate was not analyzed. According to a review by Renzi *et al*., sentinel lymph node biopsy was performed in 83 SCC patients with no clinical lymph node enlargement, and 14 (16.9%) were positive. Using multiple logistic regression analysis, the tumor size was correlated with the metastasis rate of sentinel lymph nodes (odds ratio: 4.27, $p = 0.026$).[72] According to a systematic review by Ross *et al*.,[73] metastasis was observed in sentinel lymph nodes in 139 (24%) of the 585 patients with primary anogenital SCC and in 17 (21%) of the 82 patients with non-anogenital SCC. Sentinel lymph nodes could not be identified in 20 (3%) of the 607 patients with anogenital SCC and four (3%) of the 85 patients with non-anogenital SCC. In patients who underwent lymph node dissection, sentinel lymph node biopsy was a false negative in eight (4%) of the 213 patients with anogenital SCC and one (5%) of the 20 patients with non-anogenital SCC. Ross *et al*. considered that controlled studies are necessary to evaluate whether sentinel lymph node biopsy contributes to improvement in the survival rate of SCC patients.[73] Similarly, whether sentinel lymph node biopsy in SCC patients leads to an improvement in the survival rate is not discussed in guidelines or reviews from Western countries. There have also been few studies in Japan. Maruyama *et al*. performed sentinel lymph node biopsy in 49 SCC patients and reported metastasis to sentinel lymph nodes in 18.4%.[74] Also, Takahashi *et al*. retrospectively evaluated 26 patients who underwent sentinel lymph node biopsy and reported that 23.1% were positive for metastasis to sentinel lymph nodes and that four of the six positive patients died due to SCC.[75]

From these results, although there is presently no high-level evidence concerning whether sentinel lymph node biopsy contributes to the survival of SCC patients, it appears reasonable to consider sentinel lymph node biopsy in patients considered to be at a high risk for metastasis despite the absence of abnormality in lymph nodes by physical or imaging examinations, because SCC metastasizes primarily via the lymphatic system, and because exact staging is expected to become more important in the future as novel drugs will also become available for the treatment of SCC.

1.8.5 | *Lymph node dissection*

Since the therapeutic results of SCC without regional lymph node metastasis are favorable, the presence or absence of lymph node metastasis is suggested to be an important prognostic factor. In Japan, the 80-month survival rate in the 1082 SCC patients registered at 27 facilities in 1987–1994 was 92% in stage I patients and 82.6% in stage II patients but low at 48% in stage III patients with reginal lymph node metastasis,[76] and the establishment of an effective treatment for this group is awaited. For patients demonstrated by imaging examinations in advance to have lymph node metastasis, European guidelines recommend lymph node dissection of the metastasis-positive area.[45] However, the benefits of prophylactic lymph node dissection have not been studied sufficiently, and its significance is unclear.[77] Conventionally, in Japan, prophylactic lymph node dissection for SCC has been avoided, in principle, and radical dissection has been performed when evident lymph node metastasis has been confirmed. In some non-randomized controlled studies, comparisons were made between a group that received prophylactic lymph node dissection for SCC of the face (superficial parotidectomy and cervical lymph node dissection) and a group that received tumor resection alone, and the life prognosis was reported to be more favorable in the prophylactic lymph node dissection group,[78] but none of the Western guidelines or reviews mention the benefits of prophylactic lymph node dissection. For these reasons, the clinical significance of prophylactic lymph node dissection for SCC is unclear, and the procedure is basically not recommendable.

1.8.6 | *Reconstruction*

There are various methods for reconstruction after resection, including epithelialization of the raw surface from the surrounding areas, primary plication, skin grafting, local flap, distant flap, and free flap. The reconstruction method is determined in consideration of the site, size, and depth of the defect, type of deep tissue, and functional and aesthetic aspects. Generally, an approach called reconstructive ladder devised by Harold Gillies is applied.[79] In the reconstructive ladder, reconstruction is designed by first considering a less invasive simple method, which may be conservative therapy or simple closure, and serially advancing to skin grafting, local flap, regional flap, distant flap, and free flap (Figure 1).[80] Recently, however, a theory called the reconstructive elevator, which is an approach to determine the reconstruction method by attaching more importance to functional and aesthetic aspects than the reconstructive ladder, has become the mainstay.[81] Yet, there has been no randomized control trial (RCT) that compared reconstruction methods, such as simple suture, skin grafting, and skin flaps after surgery, for SCC, and the evidence is mostly case reports.

In Japan, SCC occurs most frequently in the head and neck region (51%), followed by the trunk (9.6%), upper extremity (8.7%), and lower extremity (16.9%).[9] In 53.3% of SCC patients, the size of tumor is 2 cm or less. Since larger lesions show a greater infiltration tendency, wider resection is necessary. In patients in whom important organs (viscera, bones, and nerves) are exposed, skin grafting is difficult to select if plication is impossible,

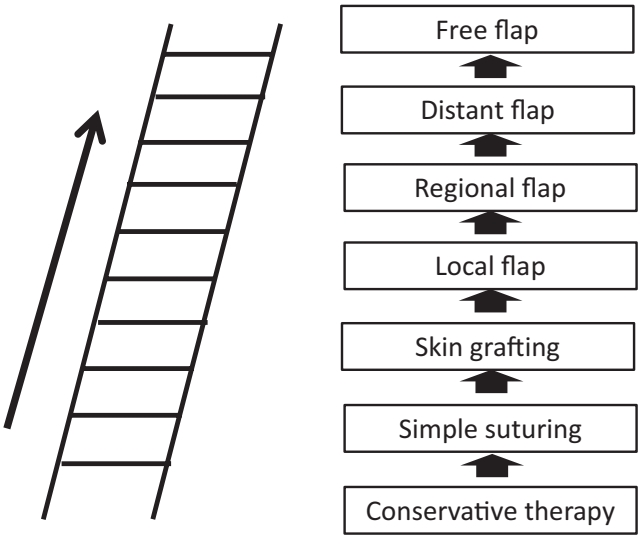

FIGURE 1 Reconstructive ladder. The reconstruction methods are evaluated serially from easier and less invasive ones as climbing the ladder step by step. This figure adapted from reference Tsuchida[80]

and reconstruction using skin flaps is required. Particularly, in the face, since organs including the eyelid, nose, ear, and mouth have characteristic structures with free margins and are exposed, aesthetic reconstruction in consideration of the thickness, color, texture, and morphology is necessary.[82] As reconstruction by unreasonable suture often results in deformity even after resection of a small area, some other techniques, such as skin grafting and local flap surgery, are often necessary. Also, more aesthetically satisfactory results mimicking the thickness, color, and texture of the natural skin are obtained by collecting the skin graft from the nearest possible site to the resected area and with full-thickness than split-thickness skin grafts. The results of skin grafting of the face using grafts from the preauricular, postauricular, supraclavicular, and infraclavicular regions vary in the order of more aesthetic to less aesthetic.

Ogata *et al.* reported that, in 325 patients with cutaneous/soft tissue malignancies (BCC in 30%, SCC in 35%, malignant melanoma in 15%, extramammary Paget's disease in 8%, and sarcoma in 6%), reconstruction was made by unreasonable suture (including major and minor amputations) in 50%, skin flap surgery in 23%, skin grafting in 24%, and a combination of skin flap and skin graft in 1%. By the site, the most frequent reconstruction method was unreasonable suture in the head and neck region (47%), upper extremity (71%), trunk (66%), lower extremity (50%), and genitalia (69%) but skin grafting in the hand and foot (65%). Skin grafting was selected most frequently for reconstruction in the hand and foot, probably because unreasonable suture causes functional impairment in the hand and foot, in which the amount of tissue is limited.[83]

Lee *et al*. performed local flap surgery in 77.7% and skin grafting in 22.3% of 153 patients with cutaneous cancer of the face (BCC in 56.8%, SCC in 37.2%, and Bowen's disease in 5.8%) for reconstruction after resection and, by conducting a questionnaire survey in 86 patients, reported that the results were more satisfactory in local flap surgery, with the satisfaction score being 4.3 and 3.5 in local flap surgery and skin grafting, respectively. They ascribed this difference in the satisfaction score to the aesthetic superiority of local flap surgery in terms of the similarly of the flap in the color and texture to the surrounding skin.[84] Concerning older patients, also, there is a report that skin flap surgery is recommended as a reconstruction method that requires fewer days for postoperative treatments.[85]

1.1.9 | Radiation therapy

1.9.1 | Introduction

In many cases, SCC stays in the primary focus, and surgery is standard therapy. However, radical radiation therapy is considered for inoperable cases, cases in which surgery is undesirable from functional and aesthetic viewpoints, cases with perineural infiltration, and locally advanced cases.[86] The results of radiation therapy in early and small SCC are favorable, and local control can be achieved in approximately 90% of the patients, similar to surgery.[87] Close cooperation between dermatologists and radiation oncologists is important for the designing of treatment.

1.9.2 | Postoperative radiation therapy

Postoperative radiation therapy is considered for patients with a positive resection margin or a resection margin near the tumor and those with perineural invasion, bone or nerve infiltration, and recurrence.[88] The radiation dose is generally 50 Gy/25–66 Gy/33 fractions. Since the frequency of lymph node metastasis is low, the usefulness of prophylactic irradiation of the lymph node region has not been established, but lymph nodes are included in the irradiation area in patients positive for lymph node metastasis. The effectiveness of the combination of chemotherapy is still under evaluation. In a retrospective study, the recurrence-free period was prolonged by concomitant administration of a platinum preparation in patients with two or more positive lymph nodes, a positive resection margin, and extranodal infiltration.[89]

1.9.3 | Radical radiation therapy for primary foci

Radical radiation therapy is effective for early disease and the local responses are excellent. Fractionated irradiation at a dose of approximately 64 Gy/32 fractions for tumors 2 cm or less in diameter and approximately 66 Gy/33 fractions for those of more than 2 cm in diameter is a standard regimen, but hypofractionated radiotherapy is also attempted. A dose of 5 Gy or higher may cause late aesthetic adverse events, but irradiation at 3 Gy to a total dose of 51–54 Gy or 2.5 Gy to a total of 50–60 Gy rarely poses aesthetic problems.[90]

Chemoradiotherapy for advanced disease is being evaluated by clinical trials, but its efficacy has not been demonstrated. Promising local effects have been reported in a phase II prospective clinical trial by weekly cisplatin administrations with irradiation at 70 Gy/35 fractions.[91]

1.9.4 | *Radical radiation therapy using special radiations*

Particle-beam radiation therapy is used for the treatment of malignant melanoma but not SCC.

1.9.5 | *Palliative radiation therapy*

Palliative irradiation for skin lesions is discussed in the CQ.

1.9.6 | *Future prospects of radiation therapy*

Electron beam therapy is performed as routine irradiation, but, for tumors with lymph node metastasis, intensity-modulated radiation therapy shows better tumor coverage and fewer complications and is considered promising. While brachytherapy has been suggested to be effective overseas, the facilities capable of this therapy are limited in Japan.

1.9.7 | *Conclusion*

As prior mentioned, close discussion between dermatologists and radiation oncologists is necessary for the determination of the extent of the tumor and volumes used for the planning of radiotherapy for SCC.

1.1.10 | Drug therapy

1.10.1 | *Introduction*

Treatment for SCC is primarily local treatment. RCT have not been performed concerning chemotherapy, and a standard treatment does not exist at present. For patients with locally advanced unresectable lesions or distant metastasis, chemotherapy similar to that for head and neck SCC is often performed.

1.10.2 | *Postoperative chemoradiotherapy*

Postoperative chemoradiotherapy is performed for high-risk SCC, but the significance of chemoradiotherapy is unclear. By comparison between radiation therapy alone and chemoradiotherapy (carboplatin 1 time/week × 6 + irradiation) in 321 patients with head and neck cancer including SCC, no significant difference was observed between the two groups.[91]

1.10.3 | *Systemic chemotherapy*

Regimens with cisplatin as the primary component are often employed in chemotherapy for SCC.[92,93] In a report of 14 patients administrated cisplatin + bleomycin + fluorouracil (5-FU), 11 responded to the treatment.[94]

Concerning molecular-targeted drugs, there is a report of cetuximab, which is effective for head and neck cancer. Maubec *et al*. administrated cetuximab alone to 36 patients with unresectable SCC and reported disease control in 25 (69%).[94]

Immune checkpoint inhibitors, a treatment established as a standard treatment for head and neck cancer, is also expected to be effective for SCC. In a phase II clinical trial of the programmed death 1 (PD-1) inhibitor cemiplimab, responses were observed in 28 (47%) of the 59 patients, and the effect persisted for 6 months or longer in 16 (57%) of the 28 treatment responders.[95] Based on these results, the US Food and Drug Administration (FDA) approved cemiplimab as a drug for SCC (September 2018). For the future, immune checkpoint inhibitors may become a standard treatment for SCC, but as SCC in immunocompromised patients after organ transplantation was excluded in this study, its use for SCC after organ transplantation requires further evaluation.

1.10.4 | *Future prospects of drug therapy*

Immune checkpoint inhibitors are the most promising as drug therapy. Their use in postoperative treatment and their combination with surgery and chemotherapy will be evaluated.

1.1.11 | Other treatments

External application of imiquimod is effective for intraepidermal cancers such as actinic keratosis and Bowen's disease (its use for diseases other than actinic keratosis of the face/hairless part of the head is uncovered by health insurance as of March 2019). External anticancer drugs (bleomycin sulfate preparation, 5-FU ointment), cryotherapy, and photodynamic therapy (PDT) are also effective as treatments for intraepidermal cancer.[96] However, the effectiveness of these treatments against infiltrative SCC is limited, and they are performed, if performed, mostly for palliation.

Mohs paste is occasionally used as a hospital preparation for the management of effusion, bleeding, and/or bad smell from tumors. This therapy degenerates or scleroses tumors with zinc oxide, which was used for tissue fixation in the original Mohs surgery.[97,98]

Also, metronidazole gel may be used for disinfection and deodorization of cancerous skin ulcers.

1.1.12 | Prognosis

Reports about the prognosis of SCC are limited. In 1987–1991, the 5-year survival rate was 99.0% in stage I, 85.0% in stage II, 65.2% in stage III (T4N0M0), 55.3% in stage III (anyTN1M0), and 38.4% (4-year survival rate) in stage IV.[99] According to the data of 1082 patients in 1987–1994 at 27 facilities, the 80-month survival rate by stage based on American Joint Committee on Cancer 2002 in 969 patients after exclusion of 113 lost to follow-up was 92% (n = 405) in stage I, 82.6% (n = 334) in stage II, 59.3% (n = 113) in stage III-1, 48% (n = 81) in stage III-2, and 48% (n = 81) in stage IV. Also, by sex, the 90-month cumulative survival rate was 73% in males and 87% in females.[8]

There are recent data from 2006 to 2012 at the National Cancer Center Hospital. As a result of 7-year follow-up of 115 SCC patients, the 5-year overall survival rate according to the UICC 2009 staging system was 100% in stage 0/I, 81.5% in stage II, 57.6% in stage III, and 0% in stage IV, and the 5-year overall survival rate calculated by the Kaplan–Meier method was 76.8%. By sex, the 5-year overall survival rate was 92.2% in females and

69.1% in males. By tissue of origin, the 5-year overall survival rate was 66.7% for scar and 78.4% for others, and it was significantly lower when SCC originated in scars,[100] partly because a higher percentage of SCC arising from burn scar are stage IV.[101] Also, according to the data of 111 SCC patients at the Department of Dermatology, Asahikawa Medical University, the 5-year overall survival rate by stage based on the UICC 2002 staging system was 100% in stage I, 79.3% in stage II, 34.4% in stage III, and 0% in stage IV.[101]

In addition, according to the data of 400 SCC patients at the Niigata Cancer Center, local recurrence was observed after treatment in 13 (3%). Also, regional lymph node metastasis was noted in 43 patients (11%) throughout the course with 23 (6%) showing metastasis at the initial treatment and 20 (5%) developing metastasis during the course. The median time until detection of lymph node metastasis during the course was 7 months. Distant metastasis was observed in nine (2%), and it was not accompanied by reginal lymph node metastasis in two (0.5%).[7] In a report examining the odds ratio of the susceptibility of various regions to metastasis of SCC compared to head and neck region, it was high at 5.86 in the external genitalia, 3.32 in the trunk, and 2.59 in the lower extremity.[9]

In the USA, the annual number of patients who develop SCC is estimated to be 180 000–520 000 with some differences among reports, and metastasis is observed in 2–5% of these patients.[19] The cure rate is reportedly 95% if the primary focus is completely resected.[102] According to a systematic review, if high-risk SCC was completely resected, the local recurrence rate was 5%, regional lymph node metastasis rate was 5%, distant metastasis rate was 1%, and mortality rate was 1%.[103]

1.1.13 | Actinic keratosis

Actinic keratosis is a precancerous lesion or intraepithelial cancer of keratinocytes that develops primarily in sun-exposed areas such as the face and dorsum of the hand. Capillary proliferation is the primary finding in an early stage, but erythema accompanied by keratinization gradually develops. By dermoscopy, slightly reddish pseudonetwork reflecting this capillary proliferation is noted, and the characteristic strawberry pattern, which shows white hyperkeratotic follicular dilatation, is observed. Actinic keratosis has five major clinical types, namely the erythematous, pigmented, verrucous, cutaneous horn, and hypertrophic types, of which the erythematous type is the commonest.[104] Histologically, atypical keratinocytes are observed primarily in the basal lamina, accompanied by solar elastosis primarily of the upper layers of the dermis. As histopathological subtypes of actinic keratosis, there are hypertrophic, atrophic, bowenoid, acantholytic, pigmented, and lichenoid types.[104]

Actinic keratosis progresses to SCC. Infiltration, inflammation, and bleeding are signs of progression to SCC.[105] There have been various reports concerning the probability of progression of actinic keratosis. For example, according to data in the USA, the probability of progression to infiltrative SCC is 0.39% in 1 year, 1.79% in 3 years, and 2.50% in 5 years,[106,107] but the figures vary widely from 0.025% to 20% a year among reports.[108]

The incidence of actinic keratosis in the Japanese population is estimated to be 100–120/100 000 people per year.[12] Actinic keratosis is more common in white populations and was relatively rare in Japanese. However, the number of patients in Japan has increased steadily with rapid aging of the population and nearly doubled from 1987 to 2001.[12]

Actinic keratosis is known to be related to chronic exposure to ultraviolet light. Concerning the preventive effect of sunscreen agents against actinic keratosis, there have been two RCT in Australian subjects, in which the incidence could be reduced by 38% and 24%, respectively.[109,110] In Japan, also, there is a cohort study of the relationship between the latitude and the incidence of skin cancer that compared the incidence of actinic keratosis between Kasai City in Hyogo Prefecture and Iejima in Okinawa Prefecture. The incidence per 100 000 people was 144.2 in Kasai City and 696.8 in Iejima, and it was five-times higher in Okinawa than in Hyogo.[111] (The latitude of Iejima is lower than that of Hyogo.) In addition, 60% of SCC in Japanese occurs in sun-exposed areas, suggesting that ultraviolet light is involved in its etiology, although not so much as in whites.[11]

Treatments for actinic keratosis include surgery, cryotherapy, PDT, external application of imiquimod, and external application of 5-FU ointment. See CQ1 for the selection of these treatments.

1.1.14 | Bowen's disease

Bowen's disease is an intraepidermal lesion of SCC, and 3–5% of the lesions are considered to progress to SCC.[112] The disease, considered to be caused by ultraviolet light, radiation, immunosuppression, and virus, is observed frequently in older individuals.[112] It is treated primarily by surgery, cryotherapy, PDT, and external application of 5-FU and imiquimod, and foreign guidelines propose selective use of these therapies depending on the site and number of lesions. The contents of the guidelines vary slightly, but surgery and cryotherapy are recommended for small lesions, and external treatments using PDT, 5-FU, and imiquimod, is recommended for large or multiple lesions. However, the conservative approach of observation with moisturization alone is also suggested for thin lesions in the lower extremities of older patients.[113]

In Japan, surgical treatment is performed widely, but evidence concerning the extent of resection is scarce. There have been reports that the local recurrence rate 1 year after resection of actinic keratosis with a margin of 1 mm was 4%[114] and that, in a retrospective study, the recurrence rate during a follow-up period of 1–5 years was 2.8%, although information concerning the margin was scarce.[115] Since the resection margin for low-risk SCC is set at 4 mm or more in CQ2 of the present guidelines, a resection margin of 1–4 mm is recommended for Bowen's disease, but further evaluation is considered necessary. In Western countries, Mohs surgery is performed widely,

but recurrence was observed in 6.3% of the 95 patients, approximately half of whom were recurrent cases, after Mohs surgery.[116] Although this procedure is considered excellent in that the resection margin can be minimized, it has not gained wide acceptance in Japan, because special training is necessary to acquire the technique, and the procedure is time- and labor-consuming. As observed above, although the evidence is insufficient, surgery is considered to be the most reliable treatment, because it provides a high local control rate and a chance for histopathological evaluation.

Cryotherapy is adopted widely primarily for mild cases because of its simplicity. Holt reported that the recurrence rate of Bowen's disease after cryotherapy was 0.5% (1/128) and that the recurrence was observed half a year after the treatment.[117] However, when Morton *et al*. compared cryotherapy and PDT, the complete response rate after one cycle of treatment was 75% in the PDT group and 50% in the cryotherapy group, and the PDT was also superior with regard to adverse events.[118] In a subsequent report, the complete response rate 12 months after treatment was 80% in the PDT group, 67% in the cryotherapy group, and 69% in the 5-FU external therapy group, also being significantly higher after PDT than after cryotherapy.[119] However, Ahmed *et al*. compared cryotherapy and curettage and reported that the recurrence rate 24 months after treatment was 13/36 in the cryotherapy group and 4/44 in the curettage group.[120] Thus, cryotherapy, which is easy to perform and is less expensive and can also be performed readily for multiple lesions, is considered a useful treatment for Bowen's disease. However, periodic check is necessary for recurrence after treatment.

There is a systematic review of treatment of Bowen's disease by PDT (uncovered by health insurance as of April 2019), and its usefulness is generally established.[121] As mentioned above, the complete response rate is higher in PDT than in cryotherapy, and according to the report by Salim *et al*.,[122] the complete response rate 12 months after treatment was 82% in PDT and 48% in external application of 5-FU with a significant difference. There are also multiple reports concerning the combination of PDT and CO_2 laser, and, according to Cai *et al*.,[123] the complete response rate was 63.63% in PDT alone but improved to 72.73% with a combination of PDT and CO_2 laser. In Japan, facilities capable of PDT are limited, and since it is not covered by health insurance as of April 2019, caution is necessary in selecting this therapy.

External therapy using 5-FU ointment has also become more prevalent than before. The recurrence rate is reported to be 8–14%,[124-126] and the response rate is slightly inferior to that in PDT as observed above. However, it is also useful as a treatment for Bowen's disease, because it is simple and applicable also to multiple lesions similar to cryotherapy.

Imiquimod (uncovered by health insurance as of April 2019) is a Toll-like receptor 7 agonist known to induce antitumor immunity. Patel *et al*.[127] reported that the complete response rate 12 weeks after treatment by external application of imiquimod was 73% without serious adverse effects, and the treatment is considered effective for Bowen's disease, but it is not covered by health insurance in Japan as of April 2019.

Clinical questions (CQs) and recommendations

CQ1 Should the following treatments be performed against actinic keratosis?

Surgery
Cryotherapy
PDT
Imiquimod
5-FU ointment
[Recommendation]
Surgery
Cryotherapy
PDT
Imiquimod
5-FU ointment

1) Surgery

For markedly keratinized lesions, lesions suspected to have intradermal infiltration, and those that have not responded to treatments other than surgery, surgical resection is recommended partly for histological confirmation.

Vote result: Strongly recommended: 7/7
Recommendation grade: 1B

2) Cryotherapy

Cryotherapy using liquid nitrogen is recommended as a simple and effective treatment.

Vote result: Strongly recommended: 7/7
Recommendation grade: 1B

3) Imiquimod

Imiquimod is recommended as a treatment for multiple lesions.

Vote result: Strongly recommended: 7/7
Recommendation grade: 1B

4) 5-FU ointment

5-Fluorouracil ointment is recommended as a treatment for multiple thin lesions.

Vote result: Strongly recommended: 7/7
Recommendation grade: 1B

5) PDT

Photodynamic therapy is recommended as a treatment for diffusely distributed multiple lesions (not covered by health insurance as of April 2019 in Japan).

Vote result: Strongly recommended: 7/7
Recommendation grade: 1B

[Background/Objective]

Actinic keratosis is an intraepithelial cancer caused by chronic exposure to sunlight and occurs primarily in the face and dorsum of the hand. Actinic keratosis is treated by surgery, cryotherapy, PDT, external application of 5-FU, and external application of imiquimod. For the selection of these treatments, guidelines based on tumor and patient factors are proposed by other countries. Despite some differences among these guidelines, they basically recommend cryotherapy or external therapy for single lesions, cryotherapy, external therapy, or PDT for multiple lesions, and surgery for markedly keratinized lesions, lesions that have not responded to other therapies, and those suspected to have intradermal infiltration. However, there are many other options, and the clinical selection of treatment is often difficult. In the present guidelines, this problem is approached by the method of EBM (evidence based medicine).

[Scientific Evidence]

Surgery is one of the most effective treatments. If the resection stump is negative, the response rate is theoretically 100%. However, because of problems, such as surgical invasion and scars, surgery should be performed by selecting patients. Although there are no reports with a high evidence level comparing surgery with other treatments in terms of the response rate, the recommendation grade was set at 1B based on the above discussion.

Cryotherapy using liquid nitrogen is a simple treatment effective for actinic keratosis. Regarding the effectiveness of cryotherapy, the complete response rate has been reported to be 68–86%.[128-133] Also, the incidence of local adverse effects has been reported to be 35–43%, and major adverse effects include pain, scarring, and depigmentation.[128,131,132,133] Since there have been many reports about cryotherapy, and since it has been performed in a large number of patients, the recommendation grade was set at 1B.

Photodynamic therapy is effective for diffusely distributed multiple lesions of actinic keratosis. Concerning its effectiveness, the local response rate has been reported to be 68–93%. The incidence of local adverse effect is reported to be relatively high at 26–100%, and they include mild adverse events such as local erythema.[128,131,132,134] Although PDT is not covered by health insurance in Japan as of March 2019, it is performed as a common treatment overseas, and a large number of cases have been reported. While no statistically significant overall difference is observed, the recommendation grade was set at 1B, because the treatment is more effective than other treatments in individual reports.

Imiquimod is used against diffusely distributed multiple lesions similarly to PDT. The complete response rate is 55–85%. The incidence of local adverse effects is relatively high at 85–92%, but they include mild adverse events, such as local erythema, as in the case of PDT.[134,135] The drug also began to be covered by health insurance in Japan in 2011. Since then, it has been used in many cases, and reports have increased, so the recommendation grade was set at 1B.

5-Fluorouracil ointment is used for diffusely distributed multiple lesions. The complete response rate is 26–96%, and the incidence of local adverse effects is relatively variable at 25–77%.[128,129,130,135,136] However, it is used widely overseas, and there are a number of reports, so the recommendation grade was set at 1B.

[Comment]

As a result of searches of the literature concerning each treatment and selection of the relevant evidence, 11 reports based on RCT were obtained. However, they varied in the subjects, and as a simple comparison of the effects of treatments per se was impossible, the complete response rate and incidence of adverse effects were evaluated as major outcomes.

Treatments not mentioned in the recommendation statements include CO_2 laser, diclofenac, and oral nicotinic acid therapy. The local disappearance rate of lesions is 72–78% in CO_2 laser, 50% in diclofenac, and not reported concerning oral nicotinic acid therapy.[133,136,137,138] Diclofenac and nicotinic acid are not covered by health insurance in Japan, and caution is needed in their use.

[Points of attention in clinical use]

Since there are many treatments for actinic keratosis, physicians should explain multiple treatments to patients before treating them. If lesions suspected to have intradermal infiltration are treated nonsurgically, a histopathological check by biopsy should be made in advance.

Of the treatments mentioned here, PDT is not covered by health insurance as of April 2019 in Japan, and caution is needed in its use. Also, imiquimod is used for the treatment of actinic keratosis, but its use in areas other than the face and hairless parts of the head is not covered by health insurance, and caution is also needed.

[Prospects of future research]

In the literature cited here, the outcomes and subjects are not uniform. Therefore, precise results will not be obtained by comparison of effects and adverse effects of the treatments per se. In the future, studies with standardization of the subjects and outcomes are required.

CQ2 How should the resection margin be determined in surgery of the primary focus of SCC?

[Recommendation]

In patients confirmed to be at a low risk, resection with a margin of 4–6 mm (or more) is strongly recommended. In other patients suspected to be at a high risk, resection with a margin of 6–10 mm (or more) is strongly recommended (See Table 2 for the risk classification).

TABLE 3 High-risk factors of squamous cell carcinoma in the National Comprehensive Cancer Network Practice Guidelines (version 1.2019)

Location and size
Trunk and extremities (excluding hands, nail units, pretibial, feet)/≥2 cm
Cheeks, forehead, scalp, neck, and pretibial/≥1 cm
"Mask areas" of face (central face, eyelids, eyebrows, periorbital, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple ear), genitalia, hands, and feet/independent of size
Clinical findings
Poorly defined borders
Site of prior radiotherapy or chronic inflammatory process
Recurrent
Rapidly growing tumor
Immunosuppression
Neurological symptoms
Pathology
Poorly differentiated
Acantholytic(adenoid), adenosquamous, desmoplastic, or metaplastic subtype
Invasion beyond subcutaneous fat
Thickness >6 mm
Perineural, lymphatic, or vascular involvement

Note: Any high-risk factor places the patient in the high-risk category.

Vote result: Strongly recommended: 7/7

Recommendation grade: 1B (low-risk group), 1C (high-risk group)

[Background/objective]

In the treatment of SCC, surgery has long been the first-line option,[139] and it is common to grossly determine the tumor margin and resect the lesion at a certain distance of normal skin ("resection margin"). In Japan, partly because Mohs surgery, which is popular in Western countries, has not gained wide acceptance, resection with a relatively wide margin has been performed for radical treatment.[140] The resection margins mentioned in the 2002 edition of "General Rules for Clinical and Pathological Studies on Malignant Neoplasms of the Skin"[141] are 2–3 cm for T4 (infiltration to cartilage, bone, and muscle.) or N1 (with regional lymph node metastasis) and 1–2 cm for other T1–T3 lesions. This was an expert opinion, and sufficient grounds were not presented. Therefore, in the Guidelines for Cutaneous Malignancies prepared since 2007,[4] this issue was reevaluated by the method of EBM.

[Scientific grounds]

Concerning the resection margin of primary lesions, there is no high-level evidence based on RCTs.

Brodland et al.[142] evaluated the resection margin in Mohs surgery and tumor clearance rate in 141 lesions of invasive primary SCC of the skin in 111 patients. The tumor clearance rate was 96% and 99% when the resection margin was 4 and 6 mm, respectively. By the tumor size, the tumor clearance rate was 100% in those <1 cm in maximum diameter (71/141, 50%) with a resection margin of 4 mm, 95% and 100% in those ≥1 cm and <2 cm in maximum diameter (41/141, 29%) with a resection margin of 4 and 6 mm, respectively, and 86%, 97%, and 100% in those ≥2 cm in maximum diameter (29/141, 21%) with a resection margin of 4, 6, and 9 mm, respectively. According to the histological grade of differentiation, the clearance rate of grade 1 lesions (104/141, 74%) was 97% and 100% with a resection margin of 4 mm and 6 mm, respectively, that of grade 2 lesions (32/141, 23%) was 93%, 97%, and 100% with a resection margin of 4, 6, and 9 mm, respectively, and that of ≥grade 3 lesions (5/141, 3%) was 80% and 100% with a resection margin of 4 and 6 mm, respectively. By the site, the clearance rate was 91%, 98%, and 100% in high-risk regions (scalp, ear, eyelid, nose, lip) (47/141) with a resection margin of 4, 6, and 9 mm, respectively, and 98% and 100% in other regions (94/141) with a resection margin of 4 and 6 mm, respectively. According to the presence or absence of subcutaneous infiltration, the clearance rate was 98% and 100% in lesions without subcutaneous infiltration (99/141) with a resection margin of 4 and 6 mm, respectively, and 90%, 98%, and 100% in lesions with subcutaneous infiltration (42/141) with a resection margin of 4, 6, and 9 mm, respectively. A resection margin of 4 mm was appropriate for most SCCs. However, the risk of wide extension of tumor was high in lesions 2 cm or greater in diameter, those showing grade 2 or more advanced histological differentiation, those showing subcutaneous infiltration, and those arising in high-risk regions. From these results, the authors concluded that a resection margin of at least 4 mm is necessary in surgery of SCC and that a margin of 6 mm is necessary for lesions 2 cm or greater in diameter, those with grade 2 or more advanced histological differentiation, those occurring in high-risk regions (head, ear, eyelid, nose, lip), and those with subcutaneous infiltration. However, they added that the above principles do not apply to recurrent SCC.

[Comment]

Primarily based on the report by Brodland et al.,[142] the English guidelines by Motley et al.[143] consider that low-risk well-circumscribed SCC <2 cm in diameter can be completely resected in 95% of the patients with a resection margin of 4 mm. A resection margin of 6 mm is recommended for larger tumors, histological grade 2 or more advanced tumors, those with subcutaneous infiltration, and those arising in high-risk areas (scalp, ear, eyelid, nose, lip).

Many of the systematic reviews and guidelines recommend a resection margin of ≥4 mm[144,145] similar to the British guidelines by Motley et al. or 4–6 mm[146-150] for low-risk groups. One set of guidelines[151] alone recommends a resection margin of ≥5 mm, but the recommendations are nearly uniform concerning low-risk groups.

For high-risk groups, recommendations differ among guidelines: besides ≥6 mm in the British guidelines, ≥9 mm,[147] a maximum of 10 mm or more,[144] 10 mm,[151,152] and Mohs surgery or CCPDMA (complete circumferential peripheral and deep margin assessment) are recommended,[146,148,150] but some guidelines do not recommend standard margins.[149,150]

In the older Japanese guidelines,[146,153] a resection margin of 4 mm was recommended for the low-risk group and 6 mm for the high-risk group. The present guidelines recommend 4–6 mm for the low-risk group and 6–10 mm for the high-risk group in consideration of the differences among systematic reviews and guidelines. However, since complete resection is impossible in some cases even by following these recommendations,[147-149] it is permitted to set a large resection margin for more assured tumor resection. This is why we expressed our recommendations as 4–6 mm (or more) for low-risk groups and 6–10 mm (or more) for high-risk groups.

[Points of attention in clinical application]

Generally, whether the tumor has been sufficiently resected or not is checked by first histologically confirming the absence of residual tumor cells in surgical specimens and, then, continuing long-term follow-up for recurrence. It is desirable to set standard resection margins that assure a high complete resection rate and low recurrence rate, but studies to the present have been conducted using the complete resection rate (tumor clearance rate) as an index.[142,147,148,149,150] If resection is incomplete, the disease will recur sooner or later, but whether cases of complete resection remain recurrence-free has not been studied. This means that standard resection margins are recommendations based on the complete resection rate and do not guarantee a low recurrence rate. Even if the resection margin is less than the standard, the research-based outcome is considered to be achieved if complete resection has been histologically confirmed, and additional resection to meet the standard resection margin is not necessarily recommended.

Some systematic reviews and guidelines[140,154,155,156] recommend CCPDMA, particularly, for high-risk groups without setting a standard resection margin. In other words, if complete resection has been made by CCPDMA, it may be unnecessary to worry about compliance with the recommendation concerning the standard margin. However, it must be remembered that the method for preparation of sections and definition of incomplete resection are not standardized among facilities. Lansbury et al.[150] systematically reviewed 118 papers and reported that 11 papers reported incomplete surgical resection but that the definition of "incomplete resection" varied among papers, in which judgments were made according to the presence of tumor cells on the resection stump, presence of tumor within 1 mm from the margin in the lateral or deeper direction, presence of tumor in a high-power field (0.5 mm), or presence of tumor on or "near" the resection stump. Concerning the method for preparation of tissue sections, Kauvar et al.[141] observed that only 1% of the stump can be examined by conventional "breadloafing" or "crisscrossing". By the common method of sectioning along the short diameter of the surgical sample and along a plane perpendicular to it, the false negative rate is unavoidably high. Also, making a judgment of "complete resection" because the section at the end of the sample is negative for tumor is not necessarily a standardized method. However, exhaustive examination of the resection stump requires circumferential sectioning of the sample, but as slightly inside the "true resection stump" is examined by this method, the probability of the judgment of a "positive stump" increases. Therefore, it must also be noted that a slightly wider resection margin is necessary to examine the stump using this method.

All guidelines set the resection margin by dividing SCC patients in to high- and low-risk groups, but the risks factors used to classify the two groups are not necessarily the same.[145] In Japan, the risk classification of the NCCN guidelines (Table 3), which is based on the site, diameter, clinical findings (border, tissue of origin, recurrence/initial episode, growth rate, presence or absence of immunosuppression, presence or absence of neurological symptoms), and histological findings (degree of differentiation, special histological type, infiltration level, tumor thickness, presence or absence of neural/vascular infiltration), is used. Minor modifications are made in these factors at each revision of the NCCN guidelines, and if this classification is applied, the settings of the resection margin for SCC change even before revision of the Japanese guidelines (or the risk classification is kept unchanged as in the previous edition without conforming to the revision of the NCCN guidelines).

Moreover, about the definition of this risk classification, it must be noted that low risk means there are none of the above risk factors and that lesions with at least one risk factor are classified as high-risk. With such criteria, many lesions of SCC are expected to be classified as high-risk lesions. In the British guidelines,[143] criteria of the high-risk groups are limited to 4 factors, i.e., site, size, histological depth, and degree of differentiation, but, if lesions that meet at least 1 of these criteria are classified as high-risk, 79% are high-risk lesions.[151] The Japanese guidelines mention 12 risk factors by mimicking the NCCN guidelines, and, if these risk factors are applied, 95.7% of the lesions are reportedly classified as high-risk.[152] If the criteria of this risk classification are applied, there is little clinical significance in classifying lesions by evaluating the risk level according to each factor, and it is more practical to list conditions of high-risk lesions and regard those that fulfill at least one of the conditions as a high-risk group. Reflecting this, the second edition of the Japanese guidelines[146] set a resection margin at "≥6 mm", in principle, but "≥4 mm" only for "cases confirmed to be at a low risk". In the present guidelines, two groups were defined as "cases confirmed to be at a low risk" and "other possibly high-risk cases".

[Prospects of future research]

For prospective studies of the resection margin for SCC, it is necessary to standardize the sample sectioning method and definition

of complete resection. Usually, the outcome is evaluated according to the complete resection rate immediately after surgery, but whether recurrence can be avoided if complete resection has been achieved is an important issue, and analysis of survival time by defining the recurrence rate as the outcome is also required. Also, the lack of uniformity of the criteria for low-risk and high-risk groups poses practical problems. It will also be necessary to evaluate the ratio between the low-risk and high-risk group when patients are classified according to the criterion that a patient with at least one risk factor is classified in a high-risk group and whether the ratio is markedly disproportionate. Furthermore, it would be even better to study the guideline compliance rate by clarifying the actual resection margin in each group and compare the histological complete resection rate or the recurrence rate after a given observation period between the guideline compliance/non-compliance groups.

CQ3 Can the following treatments recommended for unresectable SCC?

1. **Radiation therapy**
2. **Drug therapy**
   Platinum-based multi-drug chemotherapy
   Taxane-based chemotherapy
   Chemotherapy with CPT-11
   Chemotherapy with S-1
   Immune checkpoint inhibitor: cemiplimab
   Cetuximab and other EGFR inhibitors

[Recommendation]

1. There have been few studies that evaluated the therapeutic effects of radiation therapy alone, and it is difficult to precisely determine its significance. However, irradiation may be considered for palliation of symptoms depending on the patient's condition or symptoms.

   Voting results: Strongly recommended: 7/7
   Recommendation grade: 1B (medium)

2. Practically, feasible treatments are considered from the above regimens, but the use of drugs not approved by health insurance in Japan is not recommended except in clinical trial settings.

Concerning the PD-1 antibody cemiplimab, an objective response rate of 47.5% and a sustained disease control rate of 61% in patients with metastasis were reported against cutaneous SCC, in an international multicenter phase II trial. This drug was applied to the FDA of the United States for designation as an epoch-making drug and subsequently gained approval. The administration of this drug should be considered according to the systemic condition of the patient but also depending on the state of coverage by health insurance in Japan.

Voting result: Strongly recommended: 6/6
Recommendation grade: 1C (weak)

[Background/Objective]

1. Since cutaneous SCC of the skin occurs frequently in sun-exposed areas of the skin, it is often diagnosed in a stage in which the lesions are localized, and relatively favorable therapeutic results are likely to be obtained by local treatments including surgery. However, the disease may be diagnosed in an advanced stage depending on the patient background and location and judged to be unresectable. The significance, objectives, and benefits of radiation therapy in such cases were evaluated by the approach of EBM.
2. Since cutaneous SCC of the skin occurs frequently in sun-exposed areas, it is often diagnosed in a stage in which the lesions are localized, and relatively favorable therapeutic results are likely to be obtained by local treatments including surgery. However, the disease may be diagnosed in an advanced stage depending on the patient background and affected area and judged to be unresectable. The significance, objectives, and benefits of drug therapies for such cases including cytotoxic agents, molecular targeted drugs, and immune checkpoint inhibitors were evaluated by the approach of EBM.

[Scientific evidence]

1. Cutaneous SCC of the skin is fairly radiosensitive tumor, and relatively favorable therapeutic results have been reported by radiation therapy, in the setting where the lesion is localized and feasible to curative radiotherapy.[157,158] However, in all of the few studies in which radiation therapy was performed for unresectable cutaneous SCC of the skin, radiation therapy was combined with drugs such as anticancer and molecular targeted agents,[159-163] and there has been no report that evaluated the effect of radiation therapy alone against unresectable cutaneous SCC.

The evidence is presently limited to domestic general comments dealing irradiation as palliation for other cancers.[164]

2. No large-scale study concerning anticancer drugs (cytotoxic agents) has been reported, and there have only been a few relatively small retrospective studies primarily concerning multidrug chemotherapy including platinum-based ones.[93,165-167] Concerning molecular targeted drugs, two phase II clinical trials have been performed with both gefitinib[168,169] and cetuximab,[94,170] and the response rate has been reported to be 45.5%[168] and 15%[169] for gefitinib and 27.8%[94] and 31.3%[170] for cetuximab.

As for immune checkpoint inhibitors, a phase II clinical trial showed 28 (47.5%) of the 59 patients responded to PD-1 antibody

cemiplimab, and that the effect persisted for 6 months or longer in 57% of the responders.[95]

[Comment]

1. As a result of a review of the literature concerning radiation therapy for unresectable cutaneous SCC and selection of the relevant evidence, four case series reports could be retrieved. However, in none of these case series, radiation therapy was performed alone, and since it was combined with cetuximab alone[159,161,163] or multiple drugs including cetuximab,[160,162] the effect of radiation therapy alone was not evaluated, and the data could not be used for comparison of the effect of radiation therapy per se. For these reasons, in the present recommendation, radiation therapy was described as an option for palliation as in other cancers, and its recommendation grade was set at B (moderate).

Since the topic of this CQ is unresectable advanced lesions, the recommendation grade as radiation therapy intended to achieve radical cure or a comparable response is not mentioned, and the recommendation grade is restricted to the use for palliative treatment. However, since, as observed above, relatively favorable therapeutic results have been reported when the lesion is localized and radically treatable, radiation therapy is undoubtedly an important option also for achieving radical cure or complete control even in patients with lesions difficult to resect radically for reasons, such as location near the eye, and a large vessel invasion by nodal disease. It should be added that the present guidelines do not recommend against radiation therapy in such situations.

2. As a result of a review of the literature concerning drug therapy for unresectable cutaneous SCC and selection of the relevant evidence, a few reports of retrospective studies concerning cytotoxic drugs and two phase II clinical trials each of gefitinib[168,169] and cetuximab[94,170] could be retrieved. A phase II clinical trial of the PD-1 inhibitor cemiplimab, which is an immune checkpoint inhibitor, has also been performed, and its effects have been reported.[95] Based on these reports, the administration of the above drugs should be considered with comprehensive evaluation of factors including the patient's general condition. None of the above drugs is covered by health insurance for cutaneous SCC. In consideration of these points, the recommendation grade was set at C (weak).

[Points of attention in clinical application]

1. In considering radiation therapy for unresectable cutaneous SCC, it is necessary to comprehensively evaluate factors including benefits to the life prognosis and QOL, risk of complications by radiation therapy, and the patient's general condition, make judgments about the indication by consultation and discussion with radiologists, and determine the treatment goal, dose, fractions, period, radiation type, and irradiation method.
2. Based on the results of phase II clinical trials, the FDA of the United States approved cemiplimab as a treatment for cutaneous SCC. How the situation in Japan will change in the future is uncertain, but immune checkpoint inhibitors may become a standard therapy for cutaneous SCC. At present, however, none of the above drugs including cemiplimab is covered by health insurance for cutaneous SCC in Japan, and these drugs should be administered in clinical trials or similar situations with approval by the IRB of each institution.

[Prospects of future studies]

1. As observed above, there have not been clinical studies concerning the usefulness of radiation therapy for unresectable cutaneous SCC with standardized subjects or outcomes. Since radiation therapy is unlikely to be clinically performed alone, and since randomized studies are difficult to implement, the possibility that a large-scale study will be conducted in the future is considered low. The attitude to search the limited evidence for data that are of clinical use is considered necessary.
2. Cemiplimab, an immune checkpoint inhibitor, has already been approved by the FDA as a drug for cutaneous SCC. In the future, novel drugs including immune checkpoint inhibitors may also be approved in Japan as treatments for cutaneous SCC as in the case of malignant melanoma, so the trends in Japan and abroad must be carefully monitored.

CONFLICT OF INTEREST

H. Kato received a scholarship grant from Taiho Pharmaceutical.

ORCID

Shin-ichi Ansai https://orcid.org/0000-0001-7036-7084
Hiroshi Kato https://orcid.org/0000-0003-0807-1375
Toshihiro Takai https://orcid.org/0000-0001-6969-1653
Takeshi Namiki https://orcid.org/0000-0002-1092-1159
Hiroshi Koga https://orcid.org/0000-0002-0704-8037

REFERENCES

1. Sakamoto A. Squamous cell carcinoma. In: Kitagawa M, Niki T, editors. *Hyoujunn Byourigaku*, 5th edn, Tokyo: Igakushoin; 2015. p. 255 [In Japanese].
2. Squamous cell carcinoma. In: The Japanese skin cancer society, editors, *General rules for clinical and pathological studies on malignant neoplasms of the skin*, 2nd edn. Tokyo: Kanehara syuppan; 2010. p. 40–6 [In Japanese].
3. Heppt MV, Schlager G, Berking C. Epithelial precancerous lesions. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al., *Fitzpatrick's dermatology general medicine*, 9th edn. New York: McGraw-Hill; 2019. p. 1857–83.
4. Mihm MC Jr, *et al.* Actinic keratosis. In: Elder DE, *et al.*, editors. *WHO classification of skin tumours*. 4th ed. Lyon: International Agency for Research on Cancer; 2018. p. 51–2.

5. Ishihara K, Ikeda S, Mori S. The diagnosis and treatment guidelines for malignant skin tumors and the result of nationwide questionnaire. *Skin Cancer*. 1994;9:7–12 [In Japanese].
6. Ishihara K. Epidemiology of malignant skin tumors in Japan. *Skin Cancer*. 1997;12:18–25 [In Japanese].
7. Takenouchi T, Takatsuka S. Statistics of skin cancer in 1973–2010. *Journal of Niigata Cancer Center Hospital*. 2011;50:136–9 [In Japanese].
8. Ishihara K. Past statistics and prognostic factors for malignant skin tumors. *Skin Cancer*. 2007;22:209–16 [In Japanese].
9. Ishii Y, Sakaino M, Watanabe S, Kubota N, Onizawa S, Maruyama H, *et al*. A nationwide survey of squamous cell carcinoma and Bowen's disease in Japan. *Skin Cancer*. 2013;28:195–204 [In Japanese].
10. Fujisawa Y. The latest epidemiological data on skin tumors. Maruho Dermatology Seminar, 2012. http://medical.radionikkei.jp/maruho_hifuka_pdf/maruho_hifuka-121206.p [In Japanese]
11. Ishihara K. Ultraviolet and skin cancer from the point of statistical surveys, and skin damage due to ultraviolet and its countermeasures. *Biotherapy*. 2005;19:411–6 [In Japanese].
12. Ichihashi M. Photoaging. *Rinsho Derma (Tokyo)*. 2001;43:1305–12 [In Japanese].
13. NICE Guidance Skin cancer prevention. https://www.nice.org.uk/guidance/ph32
14. Work Group; Invited Reviewers, Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, Rodgers P. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78:560–78.
15. Stern RS. Prevalence of a history of skin cancer in 2007: results of an incidence-based model. *Arch Dermatol*. 2010;146:279–82.
16. Koh HK, Geller AC, Miller DR, Grossbart TA, Lew RA. Prevention and early detection strategies for melanoma and skin cancer. *Current status*. *Arch Dermatol*. 1996;132:436–43.
17. Rogers HW, Weinstock MA, Feldman SR, Coldiron BM. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the US population, 2012. *JAMA Dermatol*. 2015;151:1081–6.
18. Mansouri B, Housewright CD. The treatment of actinic keratoses-the rule rather than the exception. *JAMA Dermatol*. 2017;153:1200.
19. Baum CL, Wright AC, Martinez JC, Arpey CJ, Brewer JD, Roenigk RK, *et al*. A new evidence-based risk stratification system for cutaneous squamous cell carcinoma into low, intermediate, and high risk groups with implications for management. *J Am Acad Dermatol*. 2018;78:141–7.
20. Gloster HM Jr, Neal K. Skin cancer in skin of color. *J Am Acad Dermatol*. 2006;55:741–60; quiz 761–64.
21. Bickers DR, Lim HW, Margolis D, Weinstock MA, Goodman C, Faulkner E, *et al*. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55:490–500.
22. Saida T. Diagnosis and management of cutaneous squamous cell carcinoma. *Skin Cancer*. 1994;9:69–72 [In Japanese].
23. Friedberg EC, *et al*. *DNA repair and mutagenesis*. Washington, DC: ASM Press; 2005.
24. Lin CT, Lin WH, Lee KD. Tzeng PY DNA mismatch repair as an effector for promoting phorbol ester-induced apoptotic DNA damage and cell killing: implications in tumor promotion. *Int J Cancer*. 2006;119:1776–84.
25. Cleaver JE. Cancer in xeroderma pigmentosum and related disorders of DNA repair. *Nat Rev Cancer*. 2005;5:564–73.
26. Bangash HK, Colegio OR. Management of non-melanoma skin cancer in immunocompromised solid organ transplant recipients. *Curr Treat Options Oncol*. 2012;13:354–76.
27. Kimura K, Terui T. Malignant neoplasms of the skin - Squamous cell carcinoma, clinical diagnosis. *Nippon Rinsho*. 2013;71:479–82 [In Japanese].
28. Elder DE, Massi D, Scolyer RA, *et al*., editors. Squamous cell carcinoma. In: *WHO Classification of Skin Tumours (WHO Classification of Tumours: International Agency for Research on Cancer)*. Lyon: International Agency for Research on Cancer; 2018. p. 35–6.
29. Habif TP. Premalignant and malignant nonmelanoma skin tumors. In: Habif TP, editor. *Clinical dermatology*, 6th edn. Edinburgh, UK: Elsevier; 2015. p. 830–4.
30. Elder DE, Massi D, Scolyer RA, *et al*. editors. Premalignant keratosis. In: *WHO Classification of Skin Tumours (WHO Classification of Tumours: International Agency for Research on Cancer)*. Lyon: International Agency for Research on Cancer; 2018. p. 51–3.
31. Habif TP. Premalignant and Malignant Nonmelanoma Skin Tumors. In: Habif TP, editor. *Clinical dermatology*, 6th edn. Edinburgh, UK: Elsevier; 2015. p. 819–28.
32. Elder DE, Massi D, Scolyer RA, *et al*. editors. Squamous cell carcinoma *in situ* (Bowen disease). In: *WHO Classification of Skin Tumours (Who Classification of Tumours: International Agency for Research on Cancer)*. Lyon: International Agency for Research on Cancer; 2018. p. 46–7.
33. Murphy GF, Beer TW, Cerio R, Kao GF, Nagore E, Pulitzer MP. Squamous cell carcinoma. In: Elder DE, Massi D, Scolyer RA, Willemze R, editors. *WHO classification of Skin Tumours*, 4th edn. Lyon: International Agency for Research on Cancer; 2018. p. 35–45.
34. Cassarino DS, DeRienzo DP, Barr RJ. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification, part one. *J Cutan Pathol*. 2006;33:191–206.
35. Fukumoto D, Ansai S, Fukumoto M, Kubo Y, Arase S, Nakanishi H. A clinicopathological study of primary cutaneous squamous cell carcinoma: relationship between a new clinicopathological classification and prognosis. *Jpn J Dermatol*. 2011;121:2247–56.
36. Ackerman AB, Reddy VB, Soyer HP. *Neoplasms with follicular differentiation*. New York: Ardor Scribendi Publishers; 2001.
37. Ansai S, Fukumoto T, Kimura T. A ckinicopathological study of primary cutaneous squamous cell carcinoma. *Jpn J Dermatol*. 2008;118:29–36.
38. Nappi O, Pettinato G, Wick MR. Adenoid (acantholytic) squamous cell carcinoma of the skin. *J Cutan Pathol*. 1989;16:114–21.
39. Griffin JR, Wriston CC, Peters MS, Lehman JS. Decreased expression of intercellular adhesion molecules in acantholytic squamous cell carcinoma compared with invasive well-differentiated squamous cell carcinoma of the skin. *Am J Clin Pathol*. 2013;139:442–7.
40. Pyne JH, Myint E, Barr EM, Clark SP, David M, Na R. Acantholytic invasive squamous cell carcinoma: tumor diameter, invasion depth, grade of differentiation, surgical margins, perineural invasion, recurrence and death rate. *J Cutan Pathol*. 2017;44:320–7.
41. Cassarino DS, DeRienzo DP, Barr RJ. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification, part two. *J Cutan Pathol*. 2006;33:261–79.
42. Ansai S, Takeichi H, Arase S, Kawana S, Kimura T. Sebaceous carcinoma: an immunohistochemical reappraisal. *Am J Dermatopathol*. 2011;33:579–87.
43. Barzilai G, Greenberg E, Cohen-Kerem R, Doweck I. Pattern of regional metastases from cutaneous squamous cell carcinoma of the head and neck. *Otolaryngol Head Neck Surg*. 2005;132:852–6.
44. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Squamous cell Skin Cancer Version 2. 2018-October 5, 2017. https://oncolife.com.ua/doc/nccn/Squamous_Cell_Skin_Cancer.pdf
45. Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, *et al*. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51:1989–2007.
46. Nemzek WR, Hecht S, Gandour-Edwards R, Donald P, McKennan K. Peri-neural spread of head and neck tumors: how accurate is MR imaging? *Am J Neuroradiol*. 1998;19:701–6.

47. Sharma A, Jaiswal AA, Umredkar G, Barle R, Sharma N, Banerjee PK, *et al*. Lymph node central necrosis on the computed tomography as the predictor of the extra capsular spread in metastatic head and neck squamous cell carcinoma. *Indian J Otolaryngol Head Neck Surg*. 2017;69:323–32.
48. Hirshoren N, Olayos E, Herschtal A, Ravi Kumar AS. Gyorki DE1, preoperative positron emission tomography for node-positive head and neck cutaneous squamous cell carcinoma. *Otolaryngol Head Neck Surg*. 2017;158:122–6.
49. Cho SB, Chung WG, Yun M, Lee JD, Lee MG, Chung KY. Fluorodeoxyglucose positron emission tomography in cutaneous squamous cell carcinoma: retrospective analysis of 12 patients. *Dermatol Surg*. 2005;31:442–47.
50. Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys*. 2001;49:1061–9.
51. Weedon D, *et al*. Verrucous squamous cell carcinoma. In: LeBoit PE, *et al*. editors. *World Health Organizati classification of tumours, pathology & genetics, skin tumours*. Lyon: IARC Press; 2006. p. 22–3.
52. Murphy GF, *et al*. Verrucous squamous cell carcinoma. In: Elder DE, *et al*. editors. *WHO classification of skin tumours*, 4th edn. WHO; 2018. p. 41-2.
53. Headington JT. Verrucous carcinoma. *Cutis*. 1978;21:207–11.
54. Kirkham N, Aljefri K. Verrucous carcinoma. In: Elder DE, *et al*. editors. *Lever's histopathology of the skin*, 11th edn. Philadelphia: Wolters Kluwer, 2015. p. 1004-5.
55. Boyd AS. Verrucous carcinoma. In: Barnhill RL, *et al*. editors. *Dermatopathology*, 3rd edn. New York: McGrawHill; 2010. p. 596–8.
56. Habif TP. Benign skin tumors. In: Baxter S, editor. *Clinical dermatology*, 3rd edn. St. Louis: Mosby-year book; 1996. p. 638–9.
57. Nagano T. Dermatology seminarium – Keratoacanthoma. *Jpn J Dermatol*. 2009;199:1049–63 [In Japanese].
58. Hodak E, Jones RE, Ackerman AB. Solitary keratoacanthoma is a squamous-cell carcinoma: three examples with metastases. *Am J Dermatopathol*. 1993;15:332–42.
59. Weedon D, Haneke E, Martinka M, *et al*. Acanthomas. In: LeBoit PE, Burg G, Weedon D, Sarasin A, editors. *World health organization classification of tumours*. Lyon: IARC Press; 2006. p. 39–47.
60. Ansai S, Kimura T. Keratoacanthoma -Current topics-. Practical. *Dermatology*. 2010;32:600–6 [In Japanese].
61. Takai T, Misago N, Murata Y. Natural course of keratoacanthoma and related lesions after partial biopsy: clinical analysis of 66 lesions. *J Dermatol*. 2015;42:353–62.
62. Takai T. Advances in histopathological diagnosis of keratoacanthoma. *J Dermatol*. 2017;44:304–14.
63. Tsuchida T, Koga H, Uhara H, Japanese Skin Cancer Society. Evidence-based practice guideline for malignant skin tumors, 2nt edn. *Jpn J Dermatol*. 2015;125: 5–75 [In Japanese].
64. Ansai S, Takayama R, Kimura T, , Kawana S. Ber-EP4 is a useful marker for follicular germinative cell differentiation of cutaneous epithelial neoplasms. *J Dermatol*. 2012;39:688–92.
65. Goto K, Takai T, Fukumoto T, Anan T, Kimura T, Ansai SI, *et al*. CD117 (KIT) is a useful immunohistochemical marker for differentiating porocarcinoma from squamous cell carcinoma. *J Cutan Pathol*. 2016;43:219–26.
66. Chen ELA, Srivastava D, Nijhawan RI. Mohs micrographic surgery: development, technique, and applications in cutaneous malignancies. *Semin Plast Surg*. 2018;32:60–8.
67. Rowe DE, Caroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. *J Am Acad Dermatol*. 1992;26:976–90.
68. van Lee CB, Roorda BM, Wakkee M, Voorham Q, Mooyaart AL, de Vijlder HC, *et al*. Recurrence rates of cutaneous squamous cell carcinoma of the head and neck after Mohs micrographic surgery vs. standard excision: a retrospective cohort study. *Br J Dermatol*. 2018;181:338–43 [Epub ahead of print].
69. Leibovitch I, Huilgol SC, Selva D, Hill D, Richards S, Paver R. Cutaneous squamous cell carcinoma treated with Mohs micrographic surgery in Australia I, Experience over 10 years. *J Am Acad Dermatol*. 2005;53:253–60.
70. Fukushima S, Masuguchi S, Igata T, Harada M, Aoi J, Miyashita A, *et al*. Evaluation of sentinel node biopsy for cutaneous squamous cell carcinoma. *J Dermatol*. 2014;41:539–41.
71. Tejera-Vaquerizo A, García-Doval I, Llombart B, Cañueto J, Martorell-Calatayud A, Descalzo-Gallego MA, *et al*. Systematic review of the prevalence of nodal metastases and the prognostic utility of sentinel lymph node biopsy in cutaneous squamous cell carcinoma. *J Dermatol*. 2018;45:781–90.
72. Renzi C, Caggiati A, Mannooranparampil TJ, Passarelli F, Tartaglione G, Pennasilico GM, *et al*. Sentinel lymph node biopsy for high risk cutaneous squamouscell carcinoma: case series and review of the literature. *Eur J Surg Oncol*. 2006;25:364–9.
73. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systematic review of the English literature. *Dermatol Surg*. 2006;32:1309–21.
74. Maruyama H, Tanaka R, Fujisawa Y, Nakamura Y, Ito S, Fujimoto M. Availability of sentinel lymph node biopsy for cutaneous squamous cell carcinoma. *J Dermatol*. 2017;44:431–7.
75. Takahashi A, Imafuku S, Nakayama J, Nakaura J, Ito K, Shibayama Y. Sentinel node biopsy for high-risk cutaneous squamous cell carcinoma. *Eur J Surg Oncol*. 2014;40:1256–62.
76. Ishihara K. Statistics and prognostic factors for malignant skin tumors in Japan: malignant melanoma. *Skin Cancer*. 2005;20:234–48 [In Japanese].
77. North JH Jr, Spellman JE, Driscoll D, , Velez A, Kraybill WG, Petrelli NJ. Advanced cutaneous squamous cell carcinoma of the trunk and extremity: Analysis of prognostic factors. *J Surg Oncol*. 1997;64:212–7.
78. Xiao Y, Yuan S, Liu F, Liu B, Zhu J, He W, *et al*. Comparison between wait-and-see policy and elective neck dissection in clinically N0 cutaneous squamous cell carcinoma of head and neck. *Medicine*. 2018;97:e10782.
79. Tintle SM, Levin LS. The reconstructive microsurgery ladder in orthopaedics. *Injury*. 2013;44:376–85.
80. Tsuchida Y. Treatment of traumatic skin defects. *Rinsho Seikei Geka*. 2009;44:783–9 [In Japanese].
81. Gottlieb LJ, Krieger LM. From the reconstructive ladder to the reconstructive elevator. *Plast Reconstr Surg*. 1994;93:1503–4.
82. Badashi I, Shauly O, Lui CG, *et al*. Nonmelanoma facial skin cancer: a review of diagnostic strategies, surgical treatment, and reconstructive technique. *Clin Med Insights Ear Nose Throat*. 2019;12:1179550619865278. https://doi.org/10.1177/1179550619865278
83. Ogata D. The reconstruction technique for the skin defects after excision of skin/soft tissue malignancies. *Skin Cancer*. 2018;33:138–44 [In Japanese].
84. Lee KS, Kim JO, Kim NG, *et al*. A comparison of the local flap and skin graft by location of facial reconstruction after resetion of facial skin cancer. *Arch Craniofac Surg*. 2017;18:255–60.
85. Kimura C, Sakurai K, Ohashi K, Sugino M. Local skin flap versus skin graft after resection of malignant skin tumors of the nose. *Skin Cancer*. 2009;24:416–22 [In Japanese].
86. Alam M, Ratner D. Cutaneous squamous-cell carcinoma. *N Engl J Med*. 2001;344:975–83.
87. Kwan W, Wilson D, Moravan V. Radiotherapy for locally advanced basal cell and squamous cell carcinomas of the skin. *Int J Radiat Oncol Biol Phys*. 2004;60:406–11.
88. Strom TJ, Caudell JJ, Harrison LB. Management of BCC and SCC of the head and neck. *Cancer Control*. 2016;23:220–6.
89. Tanvetyanon T, Padha T, McCaffrey J, , Kish JA, Deconti RC, Trotti A, *et al*. Postoperative concurrent chemotherapy and radiotherapy

for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2015;37:840–5.
90. Nottage MK, Lin C, Hughes BGM, *et al*. Prospective study of definitive chemoraiation in locally or regionally advanced squamous cell carcinoma of the skin. *Head Neck*. 2017;39:679–68.
91. Porceddu SV, Bressel M, Poulsen MG, Stoneley A, Veness MJ, Kenny LM, *et al*. Postoperative concurrent chemoradiotherapy versus postoperative radiotherapy in high-risk cutaneous squamous cell carcinoma of the head and neck: the randomized phase III TROG 05.01 trial. *J Clin Oncol*. 2018;36:1275–83.
92. Jarkowski A 3rd, Hare R, Loud P, , Skitzki JJ, Kane JM, May KS, *et al*. Systemic Therapy in Advanced Cutaneous Squamous Cell Carcinoma (CSCC): the roswell park experience and a review of the literature. *Am J Clin oncol*. 2016;39:545–8.
93. Sadek H, Azli N, Wendling JL, Cvitkovic E, Rahal M, Mamelle G, *et al*. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. *Cancer*. 1990;66:1692–6.
94. Maubec E, Petrow P, Scheer-Senyarich I, Duvillard P, Lacroix L, Gelly J, *et al*. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. *J Clin Oncol*. 2011;29:3419–26.
95. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, *et al*. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Eng J Med*. 2018;379:341–51.
96. Japanese Dermatological Association and the Japanese Skin Cancer Society, editors. *Evidence-based practice guideline for malignant skin tumors*, 2nd edn. Tokyo: Kanehara Syuppan; 2015. p. 55–9.[In Japanese]
97. Ishikawa M. Management of locally advanced skin cancer. *Nippon Rinsho*. 2013;71:565–7 [In Japanese].
98. Umebayashi Y. Radiotherapy, chemotherapy and topical therapy for squamous cell carcinoma. In: Yamazaki N, *et al*. editors. *Hihukarinnsyoasetto17 Malignant tumor of the skin*. Tokyo: Nakayama syoten; 2014. p. 236–40.[In Japanese]
99. Ishihara K. The result and explanation of nationwide questionnaire. *Skin Cancer*. 1994;9:72–7 [In Japanese].
100. Omata W, Oashi K, Namikawa K, Tsutsumida A, Yamazaki N. A statistical analysis of squamous cell carcinoma at the Department of Dermatologic Oncology, National Cancer Center Hospital in Japan. *Skin Cancer*. 2013;28:154–9 [In Japanese].
101. Ito Y, Wada T, Asano K, Takahashi H, Oashi K, Namikawa K, *et al*. A statistical analysis of squamous cell carcinoma at the Department of Dermatologic Oncology, National Cancer Center Hospital in Japan. *Jpn J Dermatol*. 2002;112:961–7 [In Japanese].
102. Souza J, Clark J. Management of the neck in metastatic cutaneous squamous cell carcinoma of the head and neck. *Curr Opin Otolaryngol Head Neck Surg*. 2011;19:99–105.
103. Jambusaria-Pahlajani A, Miller CJ, Quon H, Smith N, Klein RQ, Schmults CD. Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: a systematic review of outcomes. *Dermatol Surg*. 2009;35:574–85.
104. Saida T. Diagnosis and treatment of actinic keratosis. *Skin Cancer*. 2010;25:214–31 [In Japanese].
105. Habif TP. Premalignant and Malignant Nonmelanoma Skin Tumors. In: Habif TP, editor. *Clinical dermatology*, 6th edn. Edinburgh, UK: Elsevier; 2015. p. 819–28.
106. Siegel JA, Korgavkar K, Weinstock MA. Current perspective on actinic keratosis: a review. *Br J Dermatol*. 2017;177:350–8.
107. Criscione VD, Weinstock MA, Naylor MF, Luque C, Eide MJ, Bingham SF. Department of Veteran Affairs Topical Tretinoin Chemoprevention Trial Group. I: Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer*. 2009;115:2523–30.
108. Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratosis to squamous cell carcinoma. *Lancet*. 1988;1:795–7.
109. Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med*. 1993;329:1147–51.
110. Darlington S, Williams G, Neale R, Frost C, Green A. A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol*. 2003;139:451–5.
111. Nagano T, Ueda M, Suzuki T, Naruse K, Nakamura T, Taguchi M, *et al*. Skin cancer screening in Okinawa, Japan. *J Dermatol Sci*. 1999;19:161–5.
112. Neagu TP, Ţigliş M, Botezatu D, Enache V, Cobilinschi CO, Vâlcea-Precup MS, *et al*. Clinical, histological and therapeutic features of Bowen's disease. *Rom J Morphol Embryol*. 2017;58:33–40.
113. Morton CA, Birnie AJ, Eedy DJ. British Association of Dermatologists' guidelines for the management of squamous cell carcinoma *in situ* (Bowen's disease) 2014. *Br J Dermatol*. 2014;170:245–60.
114. Hirose R, Tomimura S, Takeishi E, Yokoyama Y. A study of positive lateral margin casesin actinic keratoses. *Skin Cancer*. 2010;25:85–9 [In Japanese].
115. Hansen JP, Drake AL. Walling HW Bowen's Disease: a four-year retrospective review of epidemiology and treatment at a university center. *Dermatol Surg*. 2008;34:878–83.
116. Leibovitch I, Huilgol SC, Selva D, Richards S, Paver R. Cutaneous squamous carcinoma *in situ* (Bowen's disease): treatment with Mohs micrographic surgery. *J Am Acad Dermatol*. 2005;52:997–1002.
117. Holt PJ. Cryotherapy for skin cancer: results over a 5-year period using liquid nitrogen spray cryosurgery. *Br J Dermatol*. 1988;119:231–40.
118. Morton CA, Whitehurst C, Moseley H, McColl JH, Moore JV, Mackie RM. Comparisonof photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *Br J Dermatol*. 1996;135:766–71.
119. Morton C, Horn M, Leman J, Tack B, Bedane C, Tjioe M, *et al*. Comparison of topicalmethyl aminolevulinate photodynamic therapy with cryotherapy or Fluorouracil for treatment of squamous cell carcinoma *in situ*: Results of a multicenter randomized trial. *Arch Dermatol*. 2006;142:729–35.
120. Ahmed I, Berth-Jones J, Charles-Holmes S, O'Callaghan CJ, Ilchyshyn A. Comparison of cryotherapy with curettage in the treatment of Bowen's disease: a prospective study. *Br J Dermatol*. 2000;143:759–66.
121. Fayter D, Corbett M, Heirs M, Fox D, Eastwood A. C A systematic review of photodynamic therapy in the treatment of precancerous skin conditions, Barrett's oesophagus and cancers of the biliary tract, brain, head and neck, lung, oesophagus and skin. *Health Technol Assess*. 2010;14:1–288.
122. Salim A, Leman JA, McColl JH, Chapman R, Morton CA. Randomized comparison of photodynamic therapy with topical 5-fluorouracil in Bowen's disease. *Br J Dermatol*. 2003;148:539–43.
123. Cai H, Wang YX, Zheng JC, Sun P, Yang ZY, Li YL, *et al*. Photodynamic therapy in combination with CO2 laser for the treatment of Bowen's disease. *Lasers Med Sci*. 2015;30:1505–10.
124. Thestrup-Pedersen K, Ravnborg L, Reymann F. Morbus Bowen. A description of the disease in 617 patients. *Acta Derm Venereol*. 1988;68:236–9.
125. Bargman H, Hochman J. Topical treatment of Bowen's disease with 5-Fluorouracil. *J Cutan Med Surg*. 2003;7:101–5.
126. Sturm HM. Bowen's disease and 5-fluorouracil. *J Am Acad Dermatol*. 1979;1:513–22.
127. Patel GK, Goodwin R, Chawla M, Laidler P, Price PE, Finlay AY, *et al*. Imiquimod 5%cream monotherapy for cutaneous squamous cell carcinoma *in situ* (Bowen's disease): a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol*. 2006;54:1025–32.
128. Morton C, Horn M, Leman J, Tack B, Bedane C, Tjioe M, *et al*. Comparison of topical methyl aminolevulinate photodynamic

therapy with cryotherapy or fluorouracil for treatment of squamous cell carcinoma *in situ*. *Archiv Dermatol*. 2006;142:729–35.
129. Walker JL, Siegel JA, Sachar M, Qureshi AA, Chen SC, Swetter SM, *et al*. 5-Fluorouracil for actinic keratosis treatment and chemoprevention: a randomized controlled trial. *J invest dermatol*. 2017;137:1367–70.
130. Cunningham TJ, Tabacchi M, Eliane JP, Tuchayi SM, Manivasagam S, Mirzaalian H, *et al*. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. *J Clin Invest*. 2017;127:106–16.
131. Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, *et al*. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatolog Treat*. 2003;14:99–106.
132. Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, *et al*. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol*. 2002;47:258–62.
133. Zane C, Facchinetti E, Rossi MT, Specchia C, Ortel B, Calzavara-Pinton P. Cryotherapy is preferable to ablative CO2 laser for the treatment of isolated actinic keratoses of the face and scalp: a randomized clinical trial. *Br J Dermatol*. 2014;170:1114–21.
134. Sotiriou E, Apalla Z, Maliamani F, Zaparas N, Panagiotidou D, Ioannides D. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol*. 2009;23:1061–5.
135. Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up, British. *J Dermatol*. 2007;157:34–40.
136. Hantash BM, Stewart DB, Cooper ZA, Rehmus WE, Koch RJ, Swetter SM. Facial resurfacing for nonmelanoma skin cancer prophylaxis. *Arch Dermatol*. 2016;142:976–82.
137. Wolf JE Jr, Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratosis. *Int J Dermatol*. 2001;40:709–13.
138. Surjana D, Halliday GM, Martin AJ, Moloney FJ, Damian DL. Oral nicotinamide reduces actinic keratoses in phase II double-blinded randomized controlled trials. *J Invest Dermatol*. 2002;132:1497–500.
139. Newlands C, Currie R, Memon A, Whitaker S, Woolford T. Non-melanoma skin cancer: United Kingdom National Multidisciplinary Guidelines. *J Laryngol Otol*. 2016;130(S2):S125–S132.
140. Weinstein MC, Brodell RT, Bordeaux J, Honda K. The art and science of surgical margins for the dermatopathologist. *Am J Dermatopathol*. 2012;34:737–45.
141. Kauvar AN, Arpey CJ, Hruza G, Olbricht SM, Bennett R, Mahmoud BH. Consensus for Nonmelanoma Skin Cancer Treatment, Part II: squamous cell carcinoma, including a cost analysis of treatment methods. *Dermatol Surg*. 2015;41:1214–40.
142. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 1992;27:241–8.
143. Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol*. 2002;146:18–25.
144. Stratigos A, Garbe C, Lebbe C, Malvehy J, del Marmol V, Pehamberger H, et al. European Dermatology Forum (EDF); European Association of Dermato-Oncology (EADO); European Organization for Research and Treatment of Cancer (EORTC): Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. *Eur J Cancer*. 2015;51:1989–2007
145. Skulsky SL, O'Sullivan B, McArdle O, Leader M, Roche M, Conlon PJ, et al. Review of high-risk features of cutaneous squamous cell carcinoma and discrepancies between the American Joint Committee on Cancer and NCCN Clinical Practice Guidelines In Oncology. *Head Neck*. 2017;39:578–94.
146. Japanese Dermatological Association and the Japanese Skin Cancer Society, eds. *Evidence-based Practice Guideline for Malignant Skin Tumors*, 2nd edn. Tokyo: Kanehara syuppan;2015. p. 43-62. [In Japanese]
147. Khan AA, Potter M, Cubitt JJ, Khoda BJ, Smith J, Wright EH, et al. Guidelines for the excision of cutaneous squamous cell cancers in the United Kingdom: the best cut is the deepest. *J Plast Reconstr Aesthet Surg*. 2013;66:467–71.
148. Schell AE, Russell MA, Park SS. Suggested excisional margins for cutaneous malignant lesions based on Mohs micrographic surgery. *JAMA Facial Plast Surg*. 2013;15:337–43.
149. Ribero S, Osella Abate S, Di Capua C, Dika E, Balagna E, Senetta R, et al. Squamocellular carcinoma of the skin: clinicopathological features predicting the involvement of the surgical margins and review of the literature. *Dermatology*. 2016;232:279–84.
150. Lansbury L, Bath-Hextall F, Perkins W, Stanton W, Leonardi-Bee J. Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies. *BMJ*. 2013;347:f6153.
151. Batchelor RJ, Stables GI. An audit of the management of cutaneous squamous cell carcinoma according to the multiprofessional guidelines. *Br J Dermatol*. 2006;154:1202–3.
152. Umebayashi Y, Akama T, Manabe M. Most cases of cutaneous squamous cell carcinoma in Japan are classified as “high risk” according to the Japanese guideline. *J Dermatol*. 2012;39:812–4.
153. The Japanese Skin Cancer Society, ed. *Evidence-based Practice Guideline for Malignant Skin Tumors*, 1st edn. Kanehara syuppan;2007, p. 41-57. [In Japanese]
154. Fahradyan A, Howell AC, Wolfswinkel EM, Tsuha M, Sheth P, Wong AK. Updates on the management of non-melanoma skin cancer (NMSC). *Healthcare*. 2017;5:82.
155. Work Group; Invited Reviewers, Kim JYS, Kozlow JH, Mittal B, Moyer J, Olenecki T, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2018;78:560–78.
156. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Squamous Cell Skin Cancer. Verssion 1.2019-Augest 31, 2018.
157. Veness MJ. The important role of radiotherapy in patients with non-melanoma skin cancer and other cutaneous entities. *J Med Imaging Radiat Oncol*. 2008;52:278–86.
158. Cognetta AB, Howard BM, Heaton HP, Stoddard ER, Hong HG, Green WH. Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. *J Am Acad Dermatol*. 2012;67:1235–41.
159. Giacchero D, Barrière J, Benezery K, Guillot B, Dutriaux C, Mortier L, et al. Efficacy of cetuximab for unresectable or advanced cutaneous squamous cell carcinoma–a report of eight cases. *Clin Oncol (R Coll Radiol)*. 2011;23:716–8.
160. Kalapurakal SJ, Malone J, Robbins KT, Buescher L, Godwin J, Rao K. Cetuximab in refractory skin cancer treatment. *J Cancer*. 2012;3:257–61.
161. Preneau S, Rio E, Brocard A, Peuvrel L, Nguyen JM, Quéreux G, et al. Efficacy of cetuximab in the treatment of squamous cell carcinoma. *J Dermatol Treatment*. 2014;25:424–7.
162. Dereure O, Missan H, Girard C, Costes V, Guillot B. Efficacy and tolerance of cetuximab alone or combined with chemotherapy in locally advanced or metastatic cutaneous squamous cell carcinoma: an open study of 14 patients. *Dermatology*. 2016;232:721–30.

163. Samstein RM, Ho AL, Lee NY, Barker CA. Locally advanced and unresectable cutaneous squamous cell carcinoma: outcomes of concurrent cetuximab and radiotherapy. *J Skin Cancer*. 2014;21:2014.
164. Sasaki S. Radiotherapy for squamous cell carcinoma. *Nippon Rinsho*. 2013;71(suppl 4):517–20.
165. Ikegawa S, Saida T, Obayashi H, Sasaki A, Esumi H, Ikeda S, et al. Cisplatin combination chemotherapy in squamous cell carcinoma and adenoid cystic carcinoma of the skin. *J Dermatol*. 1989;16:227–30.
166. Shin DM, Glisson BS, Khuri FR, Clifford JL, Clayman G, Benner SE, et al. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer.J. *Clin Oncol*. 2002;20:364–70.
167. Guthrie TH Jr, Porubsky ES, Luxenberg MN, Shah KJ, Wurtz KL, Watson PR. Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: results in 28 patients including 13 patients receiving multimodality therapy. *J Clin Oncol*. 2000;23:181–4.
168. Lewis CM, Glisson BS, Feng L, Wan F, Tang X, Wistuba II, et al. A phase II study of gefitinib for aggressive cutaneous squamous cell carcinoma of the head and neck. *Clin CancerRes*. 2012;18:1435–46.
169. William WN Jr, Feng L, Ferrarotto R, Ginsberg L, Kies M, Lippman S, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: A single-arm phase II clinical trial. *J Am Acad Dermatol*. 2017;77:1110–3.
170. Foote MC, McGrath M, Guminski A, Hughes BG, Meakin J, Thomson D, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. *Ann Oncol*. 2014;25:2047–52.

How to cite this article: Ansai S-i, Umebayashi Y, Katsumata N, et al. Japanese Dermatological Association Guidelines: Outlines of Guidelines for Cutaneous Squamous Cell Carcinoma 2020. *J Dermatol*. 2021;48:e288–e311. https://doi.org/10.1111/1346-8138.15889