Received: 9 June 2023 | Accepted: 15 August 2023

DOI: 10.1111/1346-8138.16944

THE JOURNAL OF DERMATOLOGY

GUIDELINES

Japanese Dermatological Association guidelines: Outlines of Japanese clinical guidelines for basal cell carcinoma 2021

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Abstract

To summarize the current therapies for skin cancers, the Japanese Skin Cancer Society issued the first guidelines for skin cancers, including melanoma, squamous cell carcinoma, basal cell carcinoma (BCC), and extramammary Paget's disease, in 2007. These guidelines were revised in 2015. Herein, we present the English version of the 2021 edition of the Japanese clinical guidelines for BCC. In the latest edition, all procedures were performed according to the Grading of Recommendations, Assessment, Development and Evaluation systems. The clinical questions that could not be answered were selected for further analysis. A comprehensive literature search, systematic review, and recommendations for each clinical question were determined by a multidisciplinary expert panel comprising dermatologists, a plastic and reconstructive surgeon, and a pathologist. Surgical resection is the gold-standard therapy of BCC. Radiotherapy or topical treatments, other than surgical resection, have been used in some cases. Patients with unresectable or metastatic BCC require systemic therapy. Novel agents, such as immune response modifiers or hedgehog pathway inhibitors, are emerging worldwide for the treatment of BCC. Based on these viewpoints, four relevant clinical questions regarding, surgical resection, radiotherapy, topical treatment, and systemic therapy, were raised in this report that aims to help clinicians select suitable therapies for their patients.

KEYWORDS
basal cell carcinoma, grade system, guidelines, imiquimod, radiotherapy, vismodegib

This is the secondary English version of the original Japanese manuscript for "Guidelines for the management of basal cell carcinomas (2021)", published in the *Japanese Journal of Dermatology* 131: 1467–1496, 2021.

1 | INTRODUCTION

In 2007, the Japanese Skin Cancer Society issued the first edition of "Guidelines for the management of skin cancers" including melanoma, squamous cell carcinoma, basal cell carcinoma (BCC), and extramammary Paget's disease[1] in which current therapies for those skin cancers were summarized. The guidelines were updated in 2015[2] and were only available in Japanese. New diagnostic techniques in BCC, such as dermoscopy are less invasive, and non-surgical treatments are possible. Moreover, recent novel agents, such as immune response modifiers and hedgehog pathway inhibitors, are available and have proved effective for patients worldwide with BCC. Based on this evidence, the guidelines for the management of BCC have been revised and published as the 2021 Japanese basal cell carcinoma guidelines, supported by the Japanese Dermatological Association,[3] in which the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scheme (http://www.gradeworkinggroup.org/) was used. Four relevant clinical questions were raised during the Committee's deliberations regarding surgical resection, radiotherapy, topical treatment, and systemic therapy. This English version contains the clinical questions (CQs) of the updated evidence-based Japanese guidelines for BCC.

2 | PROCEDURES OF REVISION

We considered that a flexible, therapeutic clinical choice could be determined using the revised guidelines. The Japanese Basal Cell Carcinoma Guidelines Committee was formed that dermatologists, a plastic and reconstructive surgeon, and a pathologist. This version was formulated according to the method indicated in the "Minds Manual for Guideline Development 2017" in which the GRADE approach was adopted.[4] The structure of the guidelines was also reviewed: if the knowledge and techniques discussed in the CQs in the previous version were widespread and were commonly in clinical practice, such CQs were classified into "background questions" in this version. The four CQs, discussed here, which could not be answered uniquely and were not appropriate for the background questions were selected.

3 | CQS AND RELEVANT PUBLISHED WORK SEARCH

The members of the Japanese Basal Cell Carcinoma Guidelines Committee were divided into two groups: one mainly determined recommendations for each CQ (guideline development group), and the other mainly oversaw the systematic review and meta-analysis process (systematic review team). With reference to past guidelines and those from other countries, the Committee determined the main clinical issues related to the treatment of BCC and established CQs based on them. When setting out the CQs, we considered their components under the PICO system (P: patients, problems, population; I: interventions; C: comparisons, controls, comparators; O: outcomes) and conducted a comprehensive literature search based on that system. A systematic, comprehensive, published work search was performed on 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. We searched the Cochrane Library (up to issue 6, 2018), PubMed (January 1966 to June 2018), and the Japan Medical Abstracts Society (January 1983 to June 2018) databases for all CQs. If the search was insufficient, the search formulae were reviewed. Documents not included in these databases and reports from major international conferences were also manually searched and added if deemed necessary by the committee in charge of the systematic review.

After the search, two reviewers, one belonging to the systematic review team and the other not directly in charge of the CQs, independently identified important clinical issues, benefits, and harms. A secondary screening was performed on outcome-related content to determine the papers to be adopted.

4 | SYSTEMATIC REVIEW AND RECOMMENDATION FOR EACH CQ

The collected studies were systematically reviewed, and the strength of evidence was discussed by the systematic review team for each CQ, considering the strength of evidence and other factors, including risk–benefit balance and social values (Table 1). The final recommendation was determined by majority vote in an 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 agreed to pursue either direction, and the vote for the opposite direction was less than 20%. Furthermore, if 70% of the expert panel members suggested that the evidence was strong, a strong recommendation was established. Otherwise, all recommendations were set as "weak". As per the policy of the Japanese Basal Cell Carcinoma Guidelines Committee, voting for the recommendations included as many expert panel members as possible; however, those members who disclosed academic or financial conflicts of interest regarding each CQ refrained from voting for the relevant CQ.[5]

5 | OUTLINE OF THE TREATMENTS OF BASAL CELL CARCINOMA

5.1 | Surgical resection

5.1.1 | Introduction

Surgical resection has long been considered the most effective treatment of BCC in Japan.[1,2,6,7] Except for Mohs surgery, which is

TABLE 1 Strength of evidence according to the GRADE scheme.

Level	Strength of evidence	Definition
A	High	High confidence in the correlation between true and estimated effects.
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.

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

TABLE 2 Strength of recommendation according to the GRADE scheme.

Recommendation level	Definition	Description
1 (Strong) for	Do it/Recommend doing	A judgment that most well-informed people would make
2 (Weak) for	Probably do it/Suggest doing	A judgment that a majority of well-informed people would make but a substantial minority would not
3 (Weak) against	Probably not do it/ Suggest not doing	A judgment that a majority of well-informed people would not make but a substantial minority would make
4 (Strong) against	Not do it/Recommend not doing	A judgment that most well-informed people would not make

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

not popular in Japan, local recurrence can be suppressed more significantly with surgical resection than with radiotherapy, cryotherapy, or electric curettage.[8,9] Surgical resection, if feasible, is strongly recommended as the first-line treatment for BCC.

5.1.2 | Resection margin

The most important issue when selecting surgical resection is the resection margin. To set an appropriate resection margin, risk factors that affect the recurrence rate, such as clinical disease type, histological type, size, and site, must be considered.[2,10] Resection margins were considered separately for the low- and high-risk groups, as shown in Figure 1. The National Comprehensive Cancer Network (NCCN) guidelines and Japanese guidelines (first and second editions) recommend 4 mm for the low-risk group.[1,2,10] The Japanese guidelines (first and second editions) follow the NCCN guidelines; however, the grounds for 4 mm in the NCCN guidelines are based on expert opinions.[11] The NCCN guidelines for the high-risk group refer to "wider resection margins" but do not specifically specify specific margins.[10] The Japanese guidelines (second edition) stipulate that 5–10 mm should be secured, and that intraoperative rapid diagnosis and two-stage surgery should be used.

In recent years, clinical studies on resection margins have been published in Japan, although these were retrospective studies. In patients with well-defined, pigmented BCC, margins were negative in 95.3% of cases with 2-mm margins and 100% with 3-mm margins.[12] In the low-risk group, 100% of patients with 2- or 3-mm margins had negative surgical margins, and even in the high-risk group, 96.3% of patients with 3-mm margins and 88.0% with 2-mm margins had negative margins.[13] In the low-risk group, 97.3% with 2-mm margins and 98.6% with 3-mm margins, even in the high-risk group, 94.7% with 2-mm margins and 98.1% with 3-mm margins had negative surgical margins[14] Because there is not yet enough evidence on this issue, resection with wider margins should be performed based on the NCCN guidelines, with 4-mm margins in the low-risk group. If possible, intraoperative rapid diagnosis or secondary surgery in the high-risk group is recommended. However, surgery with reduced margins is permissible if a stump-free operation can be ensured. Determining tumor boundaries as accurately as possible is essential.[15]

The deep margin is also an issue when considering resection margins. Determining a deep boundary is difficult because no standard boundary site exists in the deep direction. Ultrasonography, and less commonly, reflection confocal microscopy, and optical coherence tomography to assess deep invasion may also be useful to some extent.[16–19]

Factors associated with deep invasion of BCC include histological type and tumor size.[20,21] In 694 cases of BCC, the nodular (average diameter 9.6 mm), superficial (average diameter 11.3 mm), or mixed non-aggressive types (average diameter 10.5 mm) were resected up to the subcutaneous fat tissue. Of these cases, 94.6% were negative for deep margins.[22] Conversely, only 80% of cases with mixed infiltrative or aggressive (infiltrative, micronodular, morpheaform/sclerosing, basosquamous,

	Low risk	High risk
Location/Size	Area L <20 mm	Area L ≥20 mm
	Area M <10 mm	Area M ≥10 mm
		Area H
Borders	Well defined	Poorly defined
Primary or recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior radiation therapy	(-)	(+)
Pathology		
Subtype	Nodular, superficial[1]	Aggressive growth pattern[2]
Perineural involvement	(-)	(+)

Area H = "mask areas" of the face (central face, eyelids, eyebrows, periorbital, nose, lips [cutaneous and vermilion], chin, mandible, preauricular and postauricular skin/sulci, temple, and ear), genitalia, hands, and feet.
Area M = cheeks, forehead, scalp, neck, and pretibia.
Area L = trunk and extremities (excluding the hands, nail units, pretibia, ankles, and feet).

[1] Please note that there are examples and not a comprehensive list of non-aggressive growth patterns. From BCC-B: "... and other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus".
[2] Infiltrative, micronodular, morpheaform/sclerosing, basosquamous, and BCC with carcinosarcomatous differentiation features in any portion of the tumor.

FIGURE 1 Risk factors for recurrence of basal cell carcinoma.[3,10]

or carcinosarcomatous) types were negative for deep margins, even if resected to a deeper level. Subcutaneous infiltration occurred in more than 50% of the aggressive type.[23] In addition, even in the non-aggressive (nodular, superficial, keratotic, infundibulocystic, or fibroepithelioma) type, resecting the entire nasal alar without the submucosal layer on the nasal cavity side may be necessary.[24] Furthermore, even if the histologic type was estimated through preoperative biopsy, 18% showed discrepancies with the histologic type observed in all resected specimens.[25] Of these, 40% were non-aggressive on preoperative biopsy, but were mixed with the aggressive type on total resected specimens.

The larger the tumor diameter, the deeper the resection required; however, there is insufficient evidence to determine the specific resection level.[20,21] Uniformly determining the deep margin of BCC is difficult.[11] In the low-risk group (non-aggressive small tumors), deep margins can be expected to be negative at a level that includes sufficient subcutaneous adipose tissue. The high-risk group (aggressive or large tumors) requires deeper resection; however, evidence to determine the specific resection level is insufficient.[11] Presently, the high-risk group requires deeper resection than the low-risk group; however, evidence to determine the specific level of resection is insufficient. Currently, although making adjustments according to individual cases is permissible, combining rapid intraoperative diagnosis and reconstruction after confirming pathologically negative margins, rather than performing immediate reconstruction, is desirable.

5.1.3 | Conclusion

As evidence based on the NCCN guidelines is still insufficient, a 4-mm margin should be enough to include adipose tissue in the low-risk group. In the high-risk group, if possible, a rapid intraoperative diagnosis or secondary surgery should be performed, and resection with wider margins is recommended. Surgery with reduced margins is permissible if the tumor borders are determined as accurately as possible[15] and a stump-free operation can be guaranteed.[12–14]

5.2 | Radiotherapy

5.2.1 | Introduction

BCC rarely causes distant or regional lymph node metastasis; therefore, local treatment is the mainstay. Surgical resection is often the first choice of treatment. However, based on the NCCN guidelines, radiotherapy is a curative treatment when surgical resection is not selected.[26] The 5-year local control rate of radiotherapy is as high as 93%–96%.[27–30] BCC generally occurs in the head and neck region, and problems arise when surgical resection is required. Radiotherapy is selected when (i) there are problems with functional disorders and cosmetic aspects after resection of the eyelids, nose, and auricles exist; (ii) when surgery is difficult due to the patient's general condition; or (iii) when the patient chooses radiotherapy. Radiotherapy is also used as a postoperative adjuvant therapy for patients with positive margins after resection or nerve invasion.

5.2.2 | Radiotherapy with curative intent

As shown in CQ2 of this version of the guidelines, in a randomized controlled trial (RCT) of surgery and radiotherapy for tumors that are usually considered for surgery, surgery has a higher survival

rate, lower recurrence rate, and aesthetic superiority.[31] However, many of such RCT studies include brachytherapy, which is rarely performed in Japan. As mentioned above, many reports have shown a higher rate of local control with radiotherapy for the treatment of BCC. Electron beams are generally used in radiotherapy because tumors are often thin. However, thick tumors can be treated with X-rays or a combination of X-rays and electron beams. Radiotherapy is associated with acute adverse events, such as erythema and erosion, and late adverse events that occur several months later. Late adverse events include skin hyperpigmentation, depigmentation, telangiectasia, hair loss, atrophy, scarring, and ulceration, consistent with the irradiated site[32] and may also be accompanied by osteonecrosis or cartilage necrosis.[33] As the single dose increases, the frequency of late adverse events increases. Therefore, the single dose is often administered as approximately 2 Gy to reduce the occurrence of late adverse events. Based on the NCCN guidelines, the following Gy rates are indicated: if the tumor diameter is less than 2 cm 60–64 Gy for 6–7 weeks, 50–55 Gy for 3–4 weeks, 40 Gy for 2 weeks, or five times for a total of 30 Gy for 2–3 weeks. Conversely, if the tumor is ≥2 cm in diameter and has invaded the bone or deep tissues, 60–70 Gy for 6–7 weeks or 45–55 Gy for 3–4 weeks is required. Considering late adverse events, the use of radiotherapy in young patients should be carefully considered; radiotherapy is generally recommended for patients aged ≥60 years. In addition, as absolute contraindications, hereditary diseases, such as basal cell nevus syndrome (Gorlin syndrome), which has a high risk of developing into cancer, and connective tissue diseases, such as scleroderma, are considered relative contraindications because of the high frequency of late adverse events.[34] Multiple studies have reported that more than 90% of patients are satisfied with their cosmetic appearance after radiotherapy.[35] Conversely, 60% of doctors who have treated patients have been reported to be satisfied with their patients' aesthetic appearance.[36]

5.2.3 | Radiotherapy as adjuvant therapy

The 5-year local control rate of postoperative adjuvant radiotherapy in the presence of residual tumors is 92%.[37] Regarding the irradiation schedule for postoperative adjuvant therapy, the NCCN guidelines indicate a method of administering 60–64 Gy for 6–7 weeks or 50 Gy for 4 weeks.

5.2.4 | Conclusion

As most BCCs show a good prognosis, reflecting the patient's preferences in the selection of treatment methods is easy. Radiotherapy is a non-surgical treatment; however, performing it after a thorough consultation, including the risk of late adverse events, is desirable.

5.3 | Topical therapy other than surgery or radiotherapy

5.3.1 | Introduction

In Japan, many solitary tumors include pigmented lesions and nodular BCCs. Most patients are treated surgically. Conversely, overseas, for multiple BCCs and apigmented lesions various non-surgical treatments other than surgical resection are performed and their efficacy and safety have been investigated. Among them, 5-FU ointment, cryotherapy, photodynamic therapy (PDT), and imiquimod cream have accumulated evidence as treatment methods, mainly for low-risk BCC.

5.3.2 | 5-FU ointment

The 5-FU ointment exerts antitumor effects by inhibiting thymidine synthesis. Overseas, the ointment is indicated for superficial BCCs in low-risk areas. In Japan, malignant skin tumors (squamous cell carcinoma, BCC, skin adnexal carcinoma, skin metastasis, Bowen's disease, extramammary Paget's disease, radiation keratoma, senile keratoma, erythroplasia, reticulopathy, and cutaneous metastasis of malignant lymphoma) are approved by the Japanese National Health Insurance and are among the treatment options for malignant skin tumors when surgery is difficult. Regarding the method of use, the package insert states that a 5% formulation is usually applied topically once or twice daily; in principle, performing occlusive therapy is desirable. However, evidence from Japan is scarce. In a study of 201 overseas patients with superficial BCC, topical application of 5-FU ointment twice daily for 6 weeks resulted in a disease-free rate of 74.2% after 3 years and 70.5% after 5 years.[38] For histological types other than the superficial type, recurrent cases, and high-risk sites, the cure rate with 5-FU ointment has been reported to be low, and there is a high possibility of tumors remaining in deep areas.[39–43] The main adverse events of this drug are acute inflammatory reactions at the application site, including local pain, erythema, pigmentation, and bleeding tendency. According to the above-mentioned review of 201 cases of superficial BCC, the rate of moderate or severe pain was reported to be 7% at 2 weeks of treatment and 12% at 4 weeks.[44]

5.3.3 | Cryotherapy

Cryotherapy is a treatment method that uses liquid nitrogen at −196°C and has the advantage of being simple and inexpensive. The procedure can be performed at any dermatology facility. An RCT comparing cryotherapy and radiotherapy for BCC reported that the recurrence rate after 1 year was 39% in the cryotherapy group and 4% in the radiotherapy group.[9,45,46] In an RCT of 39 patients treated with cryotherapy and 44 patients treated with PDT for superficial

and nodular BCC, the histological recurrence rate after 1 year was 15% in the cryotherapy group and 25% in the PDT group.[47] In an RCT of 58 patients in the cryotherapy group and 60 in the PDT group for superficial BCC, the 5-year recurrence rate was reported to be 20% in the cryotherapy group and 22% in the PDT group.[48] In the above two studies comparing cryotherapy and PDT, no significant difference was observed in terms of efficacy; however, cryotherapy was significantly inferior to PDT in cosmetic aspects.[47,48] In addition, there is no evidence for high-risk BCC , such as morpheaform/sclerosing, infiltrative, or recurrent types.

5.3.4 | Photodynamic therapy

Photodynamic therapy is a local therapy that utilizes thermal energy generated by applying a photosensitizer to a tumor and exposing it to excitation light. Although frequently used for skin cancers in Western countries, the application of PDT for skin cancers is not covered by Japanese National Health Insurance, but is used in clinical research at some facilities. 5-Aminolevulinic acid (ALA), its methyl acid salt, and methyl aminolevulinate (MAL) are used overseas as photosensitizers for PDT in skin cancers. 5-ALA is a δ-type amino acid with a molecular weight of 131 and a common precursor of tetrapyrrole compounds, such as heme, cytochrome, chlorophyll, vitamin B12, and bilirubin, which are required for respiratory metabolism in organisms. ALA is produced in the mitochondria, transported to the cytoplasm, metabolized sequentially to coproporphyrinogen III, taken up again into the mitochondria, and metabolized to protoporphyrin IX (PPIX). PPIX chelates divalent iron to form heme, which directly affects energy (adenosine triphosphate) production in the electron transport chain. Cancer cells take up ALA and rely on glycolysis for energy production, owing to the Warburg effect, which reduces the demand for heme. Therefore, PPIX is more likely to accumulate in cancer than in normal cells. 5-ALA does not show fluorescence; however, PPIX is fluorescent, and PDT or photodynamic diagnosis (PDD) is performed using this property.[49]

The response rate to PDT for superficial BCC is 87.4%–100%; however, the 1-year recurrence rate is 8.1%–10%, the 3-year recurrence rate, 11.6%–22%, and the 5-year recurrence rate, 22%.[50] The response rate is 50%, and the 1-year recurrence rate is 55.6% for nodular lesions.[51] Regarding the comparison of surgical resection and PDT, a placebo-controlled RCT for nodular BCC of less than 5 mm has been reported to be effective. After tumor-debulking surgery, MAL or a placebo was administered. PDT was performed, and secondary PDT was performed for refractory lesions. The pathological complete response rate was 73% in the MAL group and 21% in the placebo group.[52] In a study comparing ALA-PDT and surgical resection after tumor debulking surgery for nodular BCC, the 5-year cumulative recurrence rate was 30.7% in the ALA-PDT group and 2.3% in the surgery group.[53] A comparative trial of MAL-PDT versus surgical resection for nodular BCC also showed the superiority of surgical resection with a 5-year maintenance response rate of 76% versus 96%.[54] Two comparative trials of PDT and cryotherapy have been reported, and although no significant difference was observed in the recurrence rate, PDT was superior in cosmetic effect.[47,48]

Summarizing the results of these clinical trials, PDT has a short-term effect equivalent to that of surgical resection in the superficial type but is inferior in long-term remission maintenance effect and efficacy for the nodular type. Moreover, the therapeutic effects of PDT and cryotherapy are similar. In terms of cosmetic effects, PDT has been shown to be superior to any other treatment. In a report from Japan on the effect of PDT on BCC, 16 lesions of nodular BCC were treated with curettage, electrodeposition, and ALA-PDT, and a complete clinical response was observed in 14 lesions.[55] Histological evaluation after ALA-PDT in three cases of superficial BCC and two cases of nodular BCC of the back showed complete response in four cases and partial response in one case.[56] All studies were case reports of a small number of patients, and no long-term follow-up was performed.

5.3.5 | Imiquimod cream

Imiquimod is an imidazoquinoline-based synthetic low-molecular-weight compound whose effects are primarily induced by the stimulation of Toll-like receptors (TLR7 and 8) on monocytes, macrophages, and dendritic cells. Induction of tumor cell apoptosis is through activation of transcription factor NF-κB subunit 1, other chemokines, and inflammatory mediators that induce the expression of various cytokines (interferon α1, tumor necrosis factor, IL2, IL6, IL8, and IL12), which are believed to exert antitumor effects by inhibiting blood flow and angiogenesis. Japanese National Health Insurance has approved 5% imiquimod cream for actinic keratosis and condyloma acuminata, but not for BCC. Regarding its effectiveness alone, verifying its effectiveness and side effects alongside PDT as a treatment other than surgery in low-risk areas with a size of 0.5–2 cm is recommended overseas. Various application methods have been investigated, including single-arm and vehicle control tests.

Superficial BCC

In a prospective study of 99 patients with superficial BCC, imiquimod was administered (1) twice daily for 7 days a week, (2) once daily for 7 days a week, (3) twice daily for 3 days a week, and (4) once daily for 3 days a week for 6 weeks; resection was then performed 6 weeks after the end of treatment. In this study, the pathological cure rate was (1) 100%, (2) 87.9%, (3) 73.3%, and (4) 69.7%. A correlation exists between the frequency of treatment and effect.[57] In 128 patients, imiquimod was applied (1) twice daily, (2) once daily, (3) five times a week, and (4) three times a week for 12 weeks; resection was then performed 12 weeks after the end of treatment. The pathological cure rate was (1) 100%, (2) 87.1%, (3) 80.8%, and (4) 51.7%.[58] According to both reports, in a small number of cases where imiquimod was applied once daily or twice daily, although the pathological cure rate was high, severe skin disorders or treatment interruptions occurred in 60–70% of cases. In a large-scale, vehicle control study of 724 patients, imiquimod was administered (1) five times a week and (2) seven times a week for 6 weeks;

resection was the performed 12 weeks after the end of treatment. The pathological cure rate was (1) 82% (95% confidence interval [CI] 76%–87%) and (2) 79% (95% CI 73%–85%), respectively. No significant difference in efficacy was noted between the five and seven times per week administrations. The pathological cure rates in the vehicle group were 2% (five times a week) and 3% (seven times a week), and the imiquimod group was significantly superior in terms of efficacy.[59]

Regarding the long-term course, 169 of 182 patients were clinically evaluated 12 weeks after treatment seven times a week for 6 weeks. The healing maintenance rate was 86.3% at 1 year, 78.1% at 3 years, and 70.4% at 5 years.[60,61] In addition, among the 182 patients, 163 were clinically evaluated after 12 weeks of application five times a week for 6 weeks. The healing maintenance rates were 84.8% at 1 year, 81.8% at 3 years, and 79.7% at 5 years.[62,63]

Nodular BCC

Treatment for nodular BCC generally requires a longer period than that for the superficial type. In a prospective study of 99 patients in the 6-week group, imiquimod was administered once daily for 3 or 7 days per week, or twice daily for 3 or 7 days per week. For the 92 patients in the 12-week group, imiquimod was administered once daily for 3, 5, or 7 days per week, or twice daily for 7 days per week. The pathological cure rate 6 weeks after the end of treatment was 71% in the 6-week group and 76% in the 12-week group using the 7-day-a-week application method. In this study, both groups were unable to continue the treatment twice daily for 7 days a week owing to the strong side effects; thus, the regimen was changed to 5 days a week for 12 weeks, and the cure rate was 70%.[64] In a prospective study in which 102 patients were treated three times a week for 8 and 12 weeks, the pathological cure rate was 64.4% at 8 weeks and 71.7% at 12 weeks.[65] There are two prospective studies on imiquimod cream treatment for nodular BCC followed by Mohs surgery.[66,67] In a study comparing a group that underwent Mohs surgery after application of imiquimod five times a week for 4 weeks and Mohs surgery without imiquimod application, the median percentage increase in area from tumor size at baseline to the defect after Mohs surgery for the imiquimod group (50%; 160 mm^2) was significantly less compared with that of the control group (147%; 310 mm^2). A tendency toward fewer Mohs stages was observed in the imiquimod group, and the reconstruction time was significantly shorter in the imiquimod group, suggesting the possibility of reduced surgery.[67]

Occlusion therapy

In a prospective study on occlusion therapy with imiquimod, in which each treatment was performed for 6 weeks, the pathological cure rate was evaluated 6 weeks after the end of treatment. For the superficial type, pathological cure rates were 43% and 50% in patients with and without sealing twice a week, respectively, and 87 and 76% in patients with and without sealing thrice a week, respectively. For the nodular type, the pathological cure rates were 50% and 57% with and without sealing twice a week, respectively, and 65% and 50% with and without sealing three times a week, respectively. No statistically significant differences were noted in the effects with and without sealing.[68]

Imiquimod cream showed relatively good results in terms of cure and cure maintenance rates for the superficial subtype. The cure rate of the nodular type is not as high as that of the superficial type, and it has been shown that a long application period is required. The frequency of application is once daily and applying it 5–7 days per week for 6–12 weeks is considered optimal. Occlusive treatment has not been shown to increase efficacy, and a simple application is recommended.

5.3.6 | Summary of non-surgical/non-radiation local treatment

Surgery is the gold standard, even in Western countries, where multiple cases as well as those occurring on the trunk and extremities are common; this is obvious from Western guidelines.[10,11,69] However, considering the rapidly aging population and increasing number of ethnically diverse residents, the need for non-surgical treatment for skin cancer, particularly for BCC, will increase in the future. Therefore, as of 2019, we considered it necessary to investigate non-surgical treatment methods that can be used in Japan. Assuming that radical surgical resection is the gold standard, the effects of 5-FU ointment, liquid nitrogen cryotherapy, and PDT mentioned previously have been compared and evaluated many times in the past and are only recommended as limited treatments. 5-FU ointment is effective for superficial lesions; however, its indications are limited to nodular lesions, which are common in Japan. Liquid-nitrogen cryotherapy is equivalent to PDT in terms of efficacy and is a simple treatment that can be performed on an outpatient basis. From the perspective of recurrence rate and cosmetic aspects, liquid-nitrogen cryotherapy is positioned as a palliative treatment, and it appears that there are few merits compared with surgery.

PDT is an effective treatment for BCC, and both 5-ALA- and MAL-PDT have been used. In Japan, only porfimer sodium (Photofrin®) and talabophyrin sodium (Rezaphyrin®) have been approved as antitumor photosensitizers for PDT; their indications are early lung, esophageal, and uterine cancers, but they are not indicated for skin cancer. 5-ALA (as Alaglio® granules) has been approved as an oral drug in Japan as a diagnostic agent for "visualization of non-muscle-invasive bladder cancer during transurethral bladder tumor resection". However, it has not been approved as a topical drug for the treatment of skin cancer. In addition, the light sources used for irradiation are not evenly distributed. According to past clinical trials, tumor debulking is necessary for nodular tumors to be effective. PDT has not been approved as a drug or medical device in Japan. Therefore, we believe it would be inappropriate to refer to recommendations for PDT in this version of the guidelines as treatment options for BCC.

Regarding imiquimod cream, which is widely used as a drug and has not been clinically studied in detail as a therapeutic agent for BCC in Japan, we asked "Is imiquimod cream recommended for

patients with BCC?" We raised this as a CQ and conducted a literature and systematic review.

5.4 | Systemic chemotherapy

Basal cell carcinoma is generally cured by local treatment in 90%–99% of cases.[8,9,70,71] Even if they recur, they rarely experience regional lymph node metastasis and, even more rarely, develop distant metastases. The metastatic frequency of BCC in Japan is not accurately understood, and no accurate statistics exist worldwide. Previous reports from Western countries indicate that the metastatic frequency of BCC is 0.0028%–0.55%.[72–77]

Although BCC is common, the number of patients with metastatic and locally advanced BCC who are candidates for systemic chemotherapy is limited, and therapeutic developments have thus far been limited. Of the 34 patients enrolled in a phase I trial of cisplatin in 1978, two patients with BCC were reported, one with complete response (CR) and the other with partial response (PR).[78] Since then, several successful cases with regimens containing cisplatin have been reported.[79,80] Guthrie et al. reported in 1985 that the combination of cisplatin and doxorubicin resulted in CR in five out of eight metastatic cases of BCC and PR in two cases.[81] In 1990, the same authors also reported that of eight cases of advanced BCC, three had CR and three had PR.[82] A review article reports that the response rate of cisplatin-based chemotherapy for advanced BCC is around 80%.[83,84] However, no follow-up confirmatory studies have been conducted, and cisplatin-based chemotherapy has not yet been established as a standard treatment.

Regarding molecularly targeted drugs, the activation of hedgehog signaling has been shown to be involved in the development of BCC,[85,86] and vismodegib, which inhibits the hedgehog pathway, has been developed and has been shown in clinical trials to exert an antitumor effect against metastatic and locally advanced BCC.[87–90] Two phase II trials with vismodegib are outlined below.

5.4.1 | The ERIVANCE study

A single-arm, phase II study, named the ERIVANCE study, was performed in 104 patients, including 33 cases of BCC metastasis and 71 of locally advanced disease.[88,89] The treatment consisted of oral vismodegib (150 mg once daily), which was continued until disease progression or unacceptable adverse events. Table 3 shows the results of the primary tests.

5.4.2 | The STEVIE study

A single-arm, phase II study, the STEVIE study was performed in a total of 1215 patients, 96 with metastatic BCC and 1119 with locally advanced disease.[90] The treatment consisted of oral vismodegib (150 mg once daily), and treatment was continued until disease progression, unacceptable adverse events, or patient refusal. The main test results are shown in Table 4. Patients with Gorlin syndrome and abnormalities in the hedgehog pathway in germ cells tended to have a high response rate and long response period.

Adverse events were muscle cramps (66.4%), alopecia (61.5%), dysgeusia (54.6%), weight loss (40.6%), anorexia (24.9%), asthenia

TABLE 3 ERIVANCE study.[89]

	Objective response	Median progression free survival	Median overall survival	Adverse effect		
				G3	G4	G5
Metastatic basal cell carcinoma ($n=33$)	48.5%	9.3 months	33.4 months	35.6%	12.5%	7.7%
Locally advanced basal cell carcinoma ($n=71$)	60.3%	12.9 months	Not estimable			

Abbreviation: G, grade.

TABLE 4 STEVIE study.[90]

	Objective response		Median duration of response		Adverse effect		
	With Gorlin	Without Gorlin	With Gorlin	Without Gorlin	G3	G4	G5
Metastatic basal cell carcinoma ($n=96$)	36.9%		13.8 months		35.4%	4.5%	3.8%
	80.0%	34.2%	15.1 months	11.0 months			
Locally advanced basal cell carcinoma ($n=1119$)	68.5%		23.0 months				
	81.7%	65.6%	28.8 months	8.7 months			

Abbreviation: G, grade.

(24.0%), nausea (17.9%), loss of taste (17.5%), fatigue (16.5%), diarrhea (16.2%), arthralgia (10.2%), constipation (9.5%), vomiting (8.4%), headache (7.6%), and anemia (7.3%). Grade (G) 3, 4, and 5 adverse events with a frequency of above 1% were muscle cramps (7.7%), hair loss (1.2%), dysgeusia (2.1%), weight loss (3.9%), anorexia (1.6%), asthenia (1.8%), loss of taste (1.2%), fatigue (1.6%), anemia (1.5%), hypertension (2.2%), increased gamma-glutamyl transpeptidase (2.4%), and squamous cell carcinoma (1.2%). Treatment was discontinued in 31% of patients due to adverse events. Treatment-related deaths occurred in 46 patients (3.8%), seven of whom were judged by the attending physician to be related to vismodegib; however, the central review found no association with vismodegib in six patients, and association was unclear in one patient.

In addition, itraconazole, an antifungal drug, has also been reported to have an inhibitory effect on hedgehog signaling,[91] and a phase II trial showed that it can suppress tumor growth and reduce tumor size.[92]

6 | CLINICAL QUESTIONS AND RECOMMENDATIONS

CQ1. Curative surgical resection was performed for BCC. No tumors were exposed at the border of the permanent specimen. However, the tumor spread near the border. Is an additional surgical resection necessary?

Recommendation: Not to perform additional surgical resection is suggested.

Recommendation: 2	
Evidence level: C	
Voting results ($N = 10$)	
Benefit with strong recommendation	0/10
Benefit with weak recommendation	0/10
No benefit or risk with weak recommendation	10/10
No benefit or risk with strong recommendation	0/10
Unable to determine recommendation	0/10

6.1 | Background and purpose

Surgical resection is the gold standard treatment for BCC. According to the second edition of the guidelines for malignant skin tumors, a clinical resection margin of 5–10 mm for high-risk and 4 mm for low-risk sites is recommended,[2] which is based on reports from Western countries.[8,93]

In clinical practice, treatment is with various clinical resection margins, from 2– 10 mm, depending on the individual case. Histopathological examination of the stump in a permanent specimen may show that the histopathological extent of the tumor closely matches the clinical extent. Conversely, tumors may have a histopathological spread greater than clinical tumor spread, with exposed tumors at the surgical margins, and surgical margins are diagnosed as positive. In addition, although the pathological margins are negative, they are too narrow in some cases. If the margins are histopathologically negative, some patients are followed up without additional resection.

Discussing whether additional resection should be performed in cases where the resection margins are close to the tumor and whether the recurrence rate is tolerable even after follow-up is important. Recurrence requires re-excision and re-excision imposes a significant burden on patients. However, this process is expensive and inevitably consumes medical resources. Therefore, the recurrence rate is an important issue.

6.2 | Evidence

No articles published in Japanese journals have examined the prognosis of patients with marginal margins after BCC resection. In addition, no international articles targeting Asian patients, including Japanese, or articles on RCTs exist. We found six articles on the prognosis of close-to-stump cases and examined each of them. Pascal et al. examined the presence and absence of recurrence 10 years after resection of BCC.[94] Recurrence occurred in 1/84 cases with non-proximal margins, 14/42 cases with positive margins, and 2/17 cases with proximate margins (the tumor was close to the margin at ×400 magnification of histopathological tissue). The histological type of the BCC was not mentioned. Longhi et al. investigated the recurrence of BCC resected between 1996 and 2004 for 8 years.[95] Recurrence was observed in 0/866 of patients with non-proximal stumps and 1/40 of patients with proximate stumps (less than 1 mm). Again, the histological type of BCC was not mentioned. Lin et al. reviewed 146 cases of BCC resected between 2002 and 2013.[96] The morphea type was not included and histology involved in the study was not clearly mentioned. Recurrence after BCC resection was also investigated. For pathological margins >1 mm, recurrence was 0/77 cases, with a mean follow-up period of 5.53 years. For pathological margins <1 mm, recurrence occurred in 1/43 of cases, with a mean follow-up period of 4.48 years. Auw-Haedrich et al. investigated the prognosis of 101 periocular BCCs resected between 1997 and 1999.[97] The mean follow-up period after resection of BCC was 7.3 years (104 days to 9.7 years). Recurrence was observed in 3/18 of patients with pathological margin <0.2 mm and 1/72 patients with a pathological margin >0.2 mm. Recurrence was observed in 0/15 patients with a pathological margin <0.2 mm and in 0/59 of patients with a pathological margin >0.2 mm. When limited to the morphea type, recurrence was observed in 3/3 of cases with a pathological margin of <0.2 mm and in 1/13 of cases with a pathological margin >0.2 mm. Wavreille et al. investigated the prognosis of resected cases of BCC between 2003 and 2005.[98] By 2011, 3/11 of cases had recurrence (pathological margin >1 mm) and 8/67 of cases had recurrence (pathological margin <1 mm). Recurrence was observed in 0/47 of cases (pathological margin >0.8 mm) and 4/33 of cases (pathological margin <0.8 mm) in the nodular type. Dallari et al. investigated

recurrence after resection in 51 patients aged 75 years or older who underwent resection from September 2005 to December 2016 for head and neck BCC.[99] Recurrence was observed in 2/20 of patients with positive margins, 0/8 patients with pathological margins ≤1 mm, and 1/23 of patients with pathological margins >1 mm. The histological characteristics of each type have not yet been clarified.

The definitions of stump proximity and non-proximity differ in each study, therefore, managing the data in a unified manner is difficult. The proximity of margins was defined as a tumor close to the margin at ×400,[94] distance from margin to tumor <1 mm,[95,98,99] <0.2 mm,[97] and <0.8 mm,[98] which are inconsistent. Meta-analyses were performed based on the definitions of adjacent and non-adjacent stumps in each study. The recurrence rate was 0.48% in non-proximal stumps and 7.77% in proximal stumps. Forest plots of these results are presented in Figure 2. The risk ratio was 2.53 (95% CI 2.53–13.06), indicating that patients with close margins were more likely to relapse than patients with non-contiguous margins. When limited to the nodular type, Auw-Haedrich et al. found no recurrence in all 59 patients with a pathological margin >0.2 mm and in all 15 patients with a pathological margin <0.2 mm. These data are consistent with the clinicians' general opinion that additional resection may not be necessary if the nodular type is removed. As shown in that study, we should be aware of the data that shows that cases with close margins are more likely to recur than those with non-adjacent margins, regardless of histological type.

However, the recurrence rate in patients close to the stump was low (7.77%). Currently, we propose not performing additional resections.

6.3 | Comments

Only one study reported on survival rate.[99] In addition, no paper described costs, patient burden, or other factors. Therefore, the most important outcome was recurrence rate. Because the definitions of stump proximity and non-proximity differed in each study, handling the data in a unified manner is difficult. Regarding margin proximity, the tumor is close to the margin at ×400,[94] and the distance from the margin to the tumor is <1 mm,[95,98] <0.2 mm,[97] and <0.8 mm.[98] Therefore, the meta-analysis is unreliable.

6.4 | Salient aspects for clinical application

If surgical resection is performed for the BCC, and the tumor has spread close to the stump, is additional resection necessary? In response to this question, according to previously reported evidence, the recurrence rate in tumors close to the stump was 7.77% and that in tumors not close to the stump, 0.48%, indicating a significantly higher recurrence rate in tumors near the stump. At present, the rate is 7.77%; therefore, considering the recurrence rate as high is difficult, and we conclude that actively proceeding with re-excision is difficult. However, the advisability of re-excision should be considered after fully considering the individual circumstances, that is, the patient's age, wishes, and the risks and benefits of re-excision.

6.5 | Future study subjects

High-quality RCTs are few, particularly on Japanese patients. Therefore, a long-term follow-up study with a large number of patients is required in an RCT conducted on Japanese patients.

CQ2. Is radiotherapy recommended comparing over surgical resection for resectable BCC?

Recommendation: Not to perform radiotherapy is suggested.

Recommendation: 2	
Evidence level: C	
Voting results ($N = 9$)	
Benefit with strong recommendation	0/9
Benefit with weak recommendation	0/9
No benefit or risk with weak recommendation	8/9
No benefit or risk with strong recommendation	1/9
Unable to determine recommendation	0/9

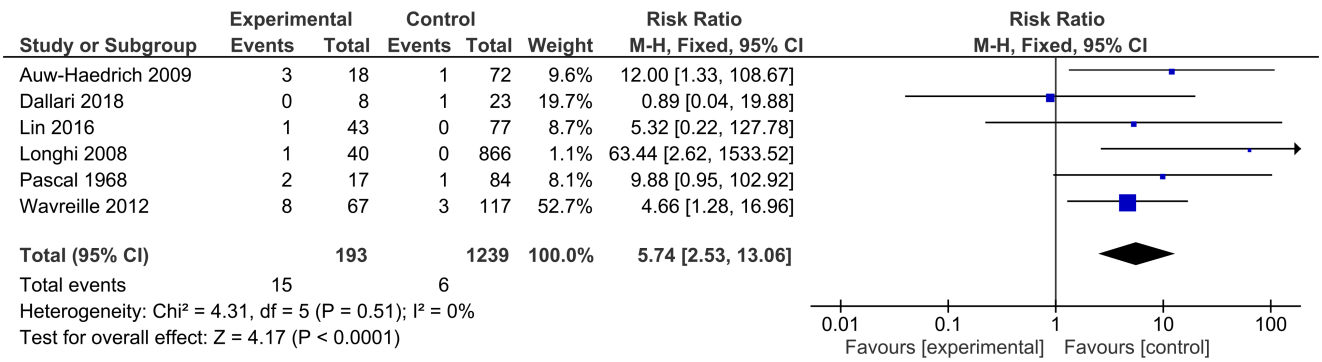

FIGURE 2 Forest plot of results.

6.6 | Background and purpose

Surgery is often the first-choice treatment of BCC. According to the NCCN guidelines,[26] a non-surgery group (receiving radiotherapy to preserve function, appearance, preference, or performance status) demonstrated the 5-year local control rate of 93%–96%, making it an option for curative treatment. In Japan, radiotherapy is selected based on the patient's condition and wishes when surgery is not indicated, that is, when surgery is difficult owing to functional and cosmetic reasons. Conversely, there is some controversy in Japan on the evaluation of surgical resection and radiotherapy for lesions for which surgery is usually selected. Verifying whether surgery or radiotherapy is recommended in terms of the cure rate and cosmetic aspects is important.

6.7 | Evidence

A literature search revealed one RCT report related to this CQ2.[31] In this study, lesions <4 cm in diameter on the face and neck were included, and the residual or recurrence rate was 0.7% after surgery and 7.5% after radiotherapy ($p = 0.003$, 95% CI 0.1–3.9). In terms of aesthetics, all evaluators of different occupations rated the surgery as superior.

6.8 | Comments

Although radiotherapy has been reported to have a high cure rate, the residual or recurrence rate is inferior to that of surgery. In addition, surgery was superior in the cosmetic evaluation, as expected. However, differences in irradiation methods exist, including brachytherapy rather than external irradiation, which is commonly performed as a method of radiotherapy in Japan. However, treatment biases exist such as those depending on the discretion of the radiation oncologist. In addition, as this study was an overseas clinical trial, careful consideration should be given to cosmetic evaluations among different races. At the panel meeting for CQ2, most opinions weakly recommended not intervening in radiotherapy. Conversely, most BCCs have a good prognosis, and although differences in survival and recurrence rates exist, radiotherapy is not excluded as a treatment option for patients.

6.9 | Salient aspects for clinical application

CQ2 is based on the recommendation of radiotherapy for operable BCC. Radiotherapy, which is administered postoperatively in some cases, remains an important treatment option. In addition, as the disease has a good prognosis, prioritizing the patient's wishes is important, and decisions should be made during discussions with the attending physician.

6.10 | Future study subjects

As no RCT of surgery and radiotherapy for operable BCC exists for the Japanese population, it is uncertain whether radiotherapy is inferior to surgery in terms of cure rate and cosmetic evaluation. In the future, we hope that RCTs will be conducted using irradiation methods in Japan.

CQ3. Is imiquimod recommended for the treatment of low-risk BCC?

CQ3A. A patient harboring low-risk BCC wishes for therapy other than surgical resection. Is imiquimod recommended over 5-FU?

Recommendation: To apply imiquimod is suggested.

Recommendation: 2	
Evidence level: C	
Voting results ($N = 10$)	
Benefit with strong recommendation	5/10
Benefit with weak recommendation	4/10
No benefit or risk with weak recommendation	1/10
No benefit or risk with strong recommendation	0/10
Unable to determine recommendation	0/10

CQ3B. Is imiquimod recommended for low-risk resectable BCC?

Recommendation: Not to apply imiquimod is suggested.

Recommendation: 2	
Evidence level: C	
Voting results ($N = 10$)	
Benefit with strong recommendation	0/10
Benefit with weak recommendation	0/10
No benefit or risk with weak recommendation	6/10
No benefit or risk with strong recommendation	4/10
Unable to determine recommendation	0/10

6.11 | Background and purpose

Surgical resection is the gold standard treatment for BCC, and radiotherapy is the first choice for non-surgical treatment. However, in Japan, where the population is aging, the number of patients who desire less invasive topical treatments among non-surgical treatments is expected to increase. In Japan, 5-FU ointments and imiquimod creams are available as topical medications to meet the needs of these patients. Although imiquimod cream has not been approved by Japanese National Health Insurance for BCC, the cream is used for actinic keratosis in clinical practice and is a topical antineoplastic agent available in Japan.

There are various circumstances in which patients desire topical treatment. These include the patient's ability to live independently, social issues, and individual preferences. However, this treatment is used for low-risk BCC. A possible CQ for such patients is whether to choose 5-FU ointment or imiquimod cream in situations where the patient does not wish to undergo surgical

resection, and topical treatment is medically acceptable. Another possible CQ is should imiquimod cream be recommended for patients with operable, low-risk BCC who desire topical treatment? These CQs are often encountered when imiquimod cream becomes available in clinical practice; therefore, the recurrence rate (long-term response rate) and side effects were evaluated as the primary outcomes.

6.12 | Evidence

Two RCTs focused on whether topical imiquimod cream is recommended for patients with BCC, comparing surgery, 5-FU ointment, and PDT. Side effects were noted in the interim reports of these trials.[38,44,100,101]

In an RCT comparing surgery for superficial and nodular BCC, 206 patients in the imiquimod group (imiquimod cream once daily for 6 weeks for the superficial type and 12 weeks for the nodular type) and 177 patients in the surgery group (resection with a 4-mm margin) were evaluated. The 5-year disease-free rates (sustained response rates) were 82.5% and 97.7% in the imiquimod and surgery groups, respectively. By histological type, the superficial type was 83.8% in the imiquimod group and 96.8% in the surgical group, and the nodular type was 81.8% in the imiquimod group and 98.8% in the surgical group.[100] Moderate-to-severe pain during treatment was reported in 27% of the superficial type, 33% of the nodular type, and 22% of the surgical group.

In an RCT comparing 5-FU ointment for superficial BCC with imiquimod, 198 patients in the imiquimod group (imiquimod cream once daily, five times a week for 6 weeks) and 201 patients in the 5-FU ointment group (twice daily for 6 weeks) were investigated. The 5-year disease-free rate was 80.5% in the imiquimod group and 70.0% in the 5-FU ointment group.[38] Pain (none/mild, moderate, and severe) at 2 weeks after treatment was 95%, 4%, and 1% in the imiquimod group, and 93%, 5%, and 2% in the 5-FU ointment group, respectively. Systemic influenza-like symptoms (4%) and wound infections (1%) were observed in the imiquimod group as systemic reactions. Erysipelas (1%), wound infections (1%), and leg ulcers (1%) were observed in the 5-FU ointment group.[44]

6.13 | Comments

Only one RCT compared surgery with 5-FU ointment, and no meta-analysis was performed. In addition, the patients' conditions were superficial and nodular, which developed in low-risk areas, and only the superficial type was found in the study that controlled the 5-FU ointment.

When comparing topical treatments, the frequency of local side effects was similar and the 5-year disease-free rate was 10.5 points higher for imiquimod cream; however, only one RCT was reported, and imiquimod cream was weakly recommended. In addition, in an RCT comparing surgery with imiquimod, surgery was superior in terms of the 5-year disease-free rate for both the superficial and nodular types (83.8% in the imiquimod group and 96.8% in the surgical group for the superficial type, and 81.8% in the imiquimod group and 98.8% in the surgical group for the nodular type). Only one RCT has been reported and surgery is weakly recommended for operable, low-risk superficial BCCs.

6.14 | Salient aspects for clinical application

Imiquimod cream is an unapproved drug for BCC in Japan. Surgical resection is the gold standard for BCC. In the disease-free rate, imiquimod cream did not show non-inferiority to surgery, even for low-risk BCC. Therefore, even in low-risk cases, surgery is recommended, if possible, and if the patient desires non-surgical external treatment, surgery should be explained first in terms of efficacy. However, the pathological cure rate for superficial BCC is 82% when applied five times a week for 6 weeks.[59] Imiquimod cream treatment should be carefully considered. Its effectiveness has also been reported for nodular BCC, which is common in Japan. The result was derived from topical application over a long period of 12 weeks; considering the actual burden of hospital visits and care for side effects, treatment with drugs alone is not a light burden on the patient. In addition, because high-risk morpheaform/sclerosing type, infiltrative type, and basal cell nevus syndromes are excluded from clinical trials, the current CQ considers recommendations only for superficial BCC. Therefore, these results cannot be applied to other pathological types of BCC.

6.15 | Future study subjects

Although the therapeutic effect of imiquimod cream alone on BCC is not comparable to that of surgery, a relatively high response rate can be expected, with a pathological cure rate of approximately 70%–80%. The application of Mohs surgery before nodular BCC has been reported to reduce the resection area.[67] For cases harboring a high risk of recurrence, we believe that conducting research on its use as a combined treatment with other drugs and radiation as well as its use as a preoperative treatment.

CQ4. Is vismodegib recommended for unresectable or metastatic BCC?

Recommendation: To perform vismodegib therapy is suggested.

Recommendation: 2	
Evidence level: C	
Voting results ($N = 10$)	
Benefit with strong recommendation	5/10
Benefit with weak recommendation	5/10
No benefit or risk with weak recommendation	0/10
No benefit or risk with strong recommendation	0/10
Unable to determine recommendation	0/10

6.16 | Background and purpose

While surgical resection is currently the first-line treatment for BCC worldwide, other local therapies, such as radiotherapy, may also be available as treatment options for recurrent and locally advanced cases. Conversely, no systemic therapy has been established for patients in whom curative local therapy is not possible. If it becomes clear that vismodegib (unapproved in Japan), a hedgehog signaling pathway inhibitor is recommended as systemic chemotherapy for unresectable, locally untreatable, or metastatic BCC, vismodegib will become the standard treatment. Vismodegib is expected to be of great help in the selection of treatment for populations for which no standard treatment has yet been established.

6.17 | Evidence

Designing a randomized study was originally difficult because no standard treatment was available, and only two single-arm studies were conducted. However, even if the study was a single-group type, the scale of the study exceeds 1000 subjects and was positioned as a confirmatory study.[89,90] The response rate was 36.4% in metastatic cases and 65.2% in locally advanced cases. Median progression-free survival (PFS) was 12.9 months [95% CI 10.2–28.0][89] and 23.2 months [95% CI 21.4–26.0].[90] A certain level of efficacy was obtained and was judged not inferior to systemic chemotherapy that has been used for other carcinomas.

6.18 | Comments

Currently, no standard treatment is available for patients with BCC who cannot be treated locally or have metastasis. No treatment group was referred to as control group and outcomes were determined through focusing on the balance between the response rate, the superiority of the PFS period, and the treatment-related adverse events due to vismodegib.

No RCT was conducted, and two single-arm intervention studies were adopted.[89,90] Response rates, median PFS, and adverse events did not differ significantly between the two studies.

The most frequently reported adverse events were muscle cramps 71.2% (G3 5.8%, G4 0%), alopecia 66.3% (G3/4 0%), dysgeusia 55.8% (G3/4 0%), weight loss 51.9% (G3 8.7%, G4 0%), and fatigue 43.3% (G3 3.8%, G4 1.0%).[89]

Currently, no standard chemotherapeutic regimen has been established for patients with advanced BCC, which is the target of this CQ. As the drug is unapproved in Japan, its administration is difficult.

6.19 | Salient aspects for clinical application

Vismodegib is an unapproved drug in Japan and access to it is currently difficult. Therefore, early approval is warranted.

6.20 | Future study subjects

We hope vismodegib will be approved for use in Japan. Furthermore, we want to conduct clinical trials to develop new treatments in which vismodegib will be used as the standard treatment in the control group.

ACKNOWLEDGMENTS

We are grateful to Mr. Shinichi Abe for assistance with the systematic literature search. The Japanese Dermatological Association funded the preparation of these guidelines. The authors did not receive any financial support from other organizations or companies.

CONFLICT OF INTEREST STATEMENT

M. S. received research funding from Mitsubishi Tanabe Pharma Corporation and Sanofi K. K. All other authors declare no conflicts of interest.

ADDENDUM

The NCCN guidelines have been updated recently.[102]

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How to cite this article: Hoashi T, Ishikawa M, Uehara J, Oashi K, Maeda S, Kato J, et al. Japanese Dermatological Association guidelines: Outlines of Japanese clinical guidelines for basal cell carcinoma 2021. J Dermatol. 2024;00:1–16. https://doi.org/10.1111/1346-8138.16944