


















GUIDELINE

Japanese Dermatological Association Guidelines: Outlines of guidelines for cutaneous melanoma 2019

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ABSTRACT

With consideration of the ongoing developments in treatment options for cutaneous melanoma, the Japanese Skin Cancer Society published the first guidelines for cutaneous melanoma in 2007 and later revised them in 2015. Here, we report on an English version of the 2019 Japanese Melanoma Guidelines. In this latest edition, all processes were carried out according to the Grading of Recommendations, Assessment, Development and Evaluation system. A comprehensive published work search, systematic review and determination of recommendations in each clinical question were performed by a multidisciplinary expert panel consisting of dermatologists, a plastic and reconstructive surgeon, and a radiation oncologist. The advent of novel agents, such as immune checkpoint inhibitors and molecular-targeted agents, has drastically changed the nature of treatment for adjuvant and advanced-stage diseases among melanoma patients worldwide. Additionally, recent reports of clinical trials regarding surgical procedures and a better understanding of molecular biology and tumor immunology in clinical types of melanoma have had an impact on clinical practise. Based on these viewpoints, eight relevant clinical questions were raised in this report that aim to help clinicians select the appropriate therapeutic approach.

Key words: cutaneous melanoma, grade system, guidelines, immune checkpoint inhibitor, molecular-targeted agent.

INTRODUCTION

In 2007, the first edition of the melanoma guidelines in Japan was published as part of the “Clinical Practise Guidelines for Skin Cancer” (Japanese version only), covering topics such as cutaneous melanoma, cutaneous squamous cell carcinoma, extramammary Paget’s disease and basal cell carcinoma. The guidelines were then subsequently revised and rereleased as a

second edition in 2015 (Japanese version only). However, the recent advent of novel agents, such as immune checkpoint inhibitors and molecular-targeted agents, has drastically changed the treatment approach for adjuvant^{1–3} or advanced-stage^{4,5} disease in our clinical practise. Recent reports of surgical clinical trials,^{6,7} including sentinel lymph node (SLN) biopsy and early completion lymph node dissection (CLND), have gradually changed the nature of treatment strategies,

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particularly for stage III melanoma patients in Japan. Under these circumstances, the guidelines for managing cutaneous melanoma have been updated and published as the 2019 Japanese Melanoma Guidelines under the support of the Japanese Dermatological Association. This article is the inaugural English version of these evidence-based Japanese guidelines for cutaneous melanoma, developed in accordance with the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) scheme (<http://www.gradeworkinggroup.org>).

PUBLISHED WORK SEARCH

Prior to a published work search, eight clinical questions (CQ) were determined by the members of the Japanese Melanoma Guidelines Committee (expert panel), considering both the recent evolutions in clinical practise for managing cutaneous melanoma and the contents of the previous version of the Japanese Melanoma Guidelines and other countries' guidelines, such as the National Comprehensive Cancer Network (NCCN) guidelines of the USA,⁸ the Cancer Council guidelines of Australia,⁹ the National Institute for Health and Care Excellence (NICE) guidelines of the UK¹⁰ and the S3 guidelines on malignant melanoma of Germany.¹¹ A systematic, comprehensive published work 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 1 January 1968 to 30 November 2017, were mainly collected using relevant key words. However, several reports that did not meet these criteria were also adopted regardless of their publication date, including non-randomized trials, retrospective studies, case series abstracts, data presented at major international meetings (e.g. American Society of Clinical Oncology, European Association of Medical Oncology) and studies reported in the Japanese language, when the committee members ruled that they should be included to determine recommendations for CQ owing to their great influence on clinical practise.

PROCESS OF GUIDELINES DEVELOPMENT

The Japanese Melanoma Guidelines Committee members consisted of 18 experts, including dermatologists, a plastic and reconstructive surgeon, and a radiation oncologist (Table S1). The eight committee members mainly oversaw the systematic review and meta-analysis process (systematic review team), and other involved individuals mainly performed the determination of recommendations for each CQ (guidelines development group) (Table S1). After creating the CQ, evidence related to each CQ was collected using relevant key words (Table S2). 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 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 Melanoma 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 refrained from 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 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

OUTLINE

The latest version of the NCCN Guidelines for Cutaneous Melanoma (version 2, published in 2019)⁸ is widely used worldwide but does not match the actual clinical practise in Japan in many regards due to differences in approved drugs, racial differences in pathophysiology and clinical types of melanoma, and differences in the health insurance system between Japan and the USA. Thus, it is necessary to establish updated guidelines for Japanese patients that suit current clinical practise. The following are the important clinical issues that the Japanese Melanoma Guidelines Committee decided to discuss.

Role and significance of surgery

The recommended surgical margins for primary melanoma are currently described in the NCCN guidelines⁸ and a previous edition of the Japanese Melanoma Guidelines (Table 3). However, these recommended surgical margins are derived from randomized controlled trials (RCT), which mainly involve Caucasians^{12–17} and include a large number of superficial spreading melanomas. Therefore, it is necessary to consider whether these guidelines are appropriate for application to melanoma patients in Japan, where acral melanoma, including subungual melanoma (SUM), is the most frequent clinical type observed. As for the surgical procedure for regional nodal basins, there are no definitive conclusions so far regarding the clinical significance of early CLND in patients with SLN metastasis in the Japanese melanoma cohort. Additionally, the appropriate extent of CLND in patients with regional lymph node metastases remains unclear. Clinical evidence should be validated based on comprehensive published work research.

Adjuvant therapy and postoperative follow up

To reduce postoperative recurrence and metastasis after curative surgery, there are multiple treatment modalities available for adjuvant therapy, including systemic therapies, such as immune checkpoint inhibitors and molecular-targeted agents, and local therapies, such as radiotherapy. However, the efficacy, significance and appropriate selection of these adjuvant therapies are not clearly defined in the context of Japanese melanoma patients. Further, the early detection of recurrence and metastasis during the postoperative follow-up period has become more important than ever owing to the development of effective novel agents for advanced-stage cases. Thus far, there is no consensus established for the nature of postoperative follow up, including the appropriate intervals of medical

Table 3. Peripheral surgical margins for wide excision for primary cutaneous melanoma recommended in the previous version of the Japanese Melanoma Guidelines

Tumor thickness	Recommended peripheral margins
<i>In situ</i>	0.3–0.5 cm
≤1.0 mm	1 cm
1.01–2 mm	1–2 cm
2.01–4 mm	2 cm
>4 mm	2 cm

examination and the ideal timing for the workup of radiological imaging.

Determination of treatment options for distant metastases

Immune checkpoint inhibitors and molecular-targeted agents are widely accepted for use in advanced cases. The Japanese Skin Cancer Society recently released the updated version of “Guidance of Drug Therapy for Melanoma” (version 1, Japanese version only, published in 2019)¹⁸ based on the latest situation of drug approval in Japan (Fig. 1). Meanwhile, multiple treatment modalities, including surgery, radiotherapy and drug therapy, must be considered comprehensively as treatment options in patients with melanoma brain metastasis (MBM), which would depend on the number, size and site(s) of such. The other need that exists is the establishment of a more accurate detection technique of *BRAF*^{V600} mutations. As the proportion of Japanese melanoma patients harboring *BRAF*^{V600} mutations is approximately 30%,¹⁹ which is lower than that of the Caucasian population, increasing the accuracy of the detection of *BRAF*^{V600} mutations will be of great help to Japanese melanoma patients in order to increase the treatment options in both adjuvant and advanced settings.

Based on the outline described above, the Japanese Melanoma Guidelines Committee established the following eight CQ (Table 4).

CLINICAL QUESTIONS AND RECOMMENDATIONS

CQ1. Is non-amputative digit-preservation surgery recommended for patients with invasive subungual melanoma?

Recommendation: Not to perform non-amputative digit preservation surgery is suggested in patients with subungual melanoma.

Recommendation: 2

Evidence level: C

Agreement rate: 69% (9/13)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	23% (3/13)	0	69% (9/13)	8% (1/13)

Background and purpose

The NCCN Guidelines for Cutaneous Melanoma (version 2, published in 2019)⁸ and the previous version of the Japanese Melanoma Guidelines contain recommended peripheral margins for the wide excision of primary cutaneous melanoma. These recommended peripheral margins are based on the

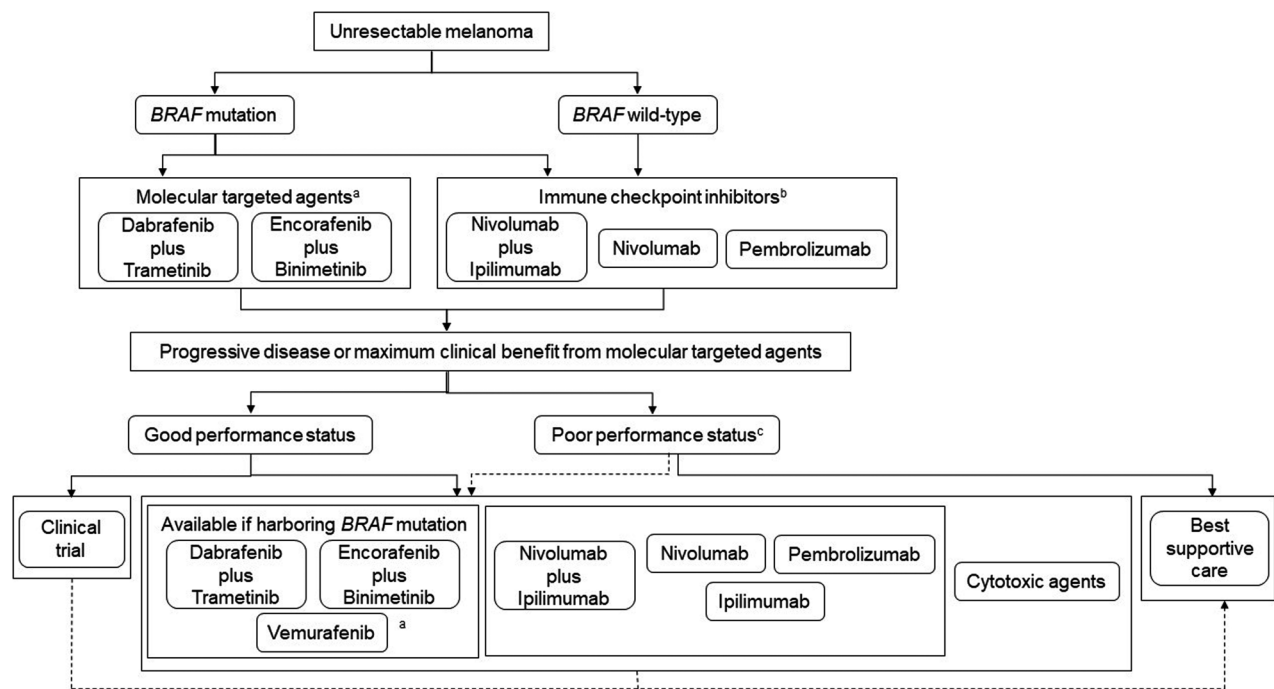


Figure 1. English translation version of the Japanese “Guidance of Drug Therapy for Melanoma” (version 1, published in 2019). (a) Application of *BRAF* inhibitors alone should be considered only when severe comorbidity prevents patients from receiving the combination targeted therapy. (b) According to the Proper Use Guide in Japan, nivolumab/ipilimumab combination therapy is proposed only when less than 1% of programmed death ligand 1 expression on the tumor cells is observed. (c) If visceral metastases lead to the deterioration of performance status, drug therapy for metastatic disease should be considered.

results of several phase III randomized clinical trials comparing narrow and wider peripheral margins that mainly included Caucasian populations.^{12–17} Very few cases of acral melanoma

Table 4. Summary of clinical questions

Role and significance of surgery

- CQ1. Is non-amputative digit-preservation surgery recommended for patients with invasive subungual melanoma?
- CQ2. Is completion lymph node dissection recommended for patients with sentinel lymph node metastasis?
- CQ3. Should additional iliac and obturator lymph node dissection be performed in patients who need inguinal lymph node dissection?

Adjuvant therapy and postoperative follow up

- CQ4. Should postoperative adjuvant radiotherapy be considered after regional lymph node dissection for patients with stage III disease?
- CQ5. Should adjuvant systemic therapies be performed for patients with resected stage III or IV melanoma?
- CQ6. Should there be periodic imaging tests performed in the follow-up period after curative resection?

Determination of treatment options for advanced stage

- CQ7. Are novel agents recommended for the treatment of melanoma brain metastases?
- CQ8. Which tumor samples of primary or metastatic melanoma should be chosen for appropriate genetic testing of *BRAF*^{V600} mutation?

were enrolled in these clinical trials, making it unclear as to whether the peripheral margins recommended in the guidelines should be applied to patients with acral melanoma. Additionally, there are no recommendations regarding deep margins included in the current guidelines. Amputation surgery has been considered a reasonable procedure and is still being selected for most patients with SUM because relatively wide peripheral margins for the digital skin are recommended in these guidelines, and the distance from the base of the tumor to the underlying distal phalanx is usually narrow. In contrast, the non-amputative digit-preservation surgery (NADPS), in which the primary tumor is dissected over the cortical bone of the distal phalanx, is increasingly becoming common for patients with thin- to intermediate-thickness SUM.^{20–23} However, these surgical procedures must be appropriately applied based on evidence.

Evidence

There were only four retrospective observational studies available in the published work comparing amputation surgery with NADPS.^{23–26} A meta-analysis including these four studies demonstrated that the performance of amputation surgery reduced local recurrence rates when compared with NADPS, but not in a statistically significant fashion (12.6% vs 8.9%; risk ratio, 0.63; 95% confidence interval (CI), 0.12–3.27; *P* = 0.58). No studies appeared to compare the positive-margin rate, overall survival (OS) or postoperative morbidity between the amputation surgery group and NADPS group.

Comments

There have been no previous meta-analyses, RCT or prospective studies completed investigating the non-inferiority of NADPS in comparison with amputation surgery in terms of relapse-free survival (RFS), local recurrence rate, OS, positive-margin rate or postoperative complications. Although four retrospective studies^{23–26} focused on the RFS and local recurrence rate, patient backgrounds and characteristics were largely heterogeneous among those studies. Further, a meta-analysis of those four studies indicated that there was no significant difference in the local recurrence rates following NADPS and amputation surgery, respectively, but the strength of evidence of the meta-analysis, due to containing a limited number of studies, was low. There were few studies that focused on differences in the OS between the NADPS and amputation groups, and no retrospective studies investigated the differences in the positive-margin rate or postoperative complications. Although NADPS may improve the quality of life (QOL), a high strength of evidence does not exist to strongly support recommending NADPS. Thus, the Japanese Melanoma Guidelines Committee cannot actively recommend an intervention to be pursued using NADPS among patients with invasive SUM at this time.

Salient aspects for clinical application

Considering the current strength of evidence, NADPS should not be generally offered to patients with invasive SUM. Where appropriate, this procedure should be performed by well-experienced, skillful dermatological surgeons. Additionally, the adequate selection of patients who are suitable to undergo this procedure is imperative so as to obtain successful treatment results (e.g. a high rate of negative-margin excision). Therefore, this procedure should be offered as a prospective clinical trial performed by well-experienced dermatological surgeons only when a patient strongly requests to pursue digit preservation.

Study subjects in the future

To our knowledge, there have been no reports made of prospective clinical trials evaluating the efficacy and safety of NADPS. Because of the rarity of invasive SUM, RCT for the evaluation of the efficacy and safety of NADPS would be unfeasible. A confirmatory single-arm prospective study comparing the historical control of amputation surgery with NADPS may be a more feasible trial design. Recent phase Ib to II clinical trials investigating the efficacy of neoadjuvant therapy using immune checkpoint inhibitors and molecular-targeted agents demonstrated a high rate of preoperative pathological response. Further development of these neoadjuvant regimens may enhance the scope of the application of NADPS among invasive melanoma patients.

CQ2. Is CLND recommended for patients with SLN metastasis?

Recommendation: Not to perform CLND is suggested in patients with SLN metastasis.

Recommendation: 2

Evidence level: B

Agreement rate: 86% (12/14)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	7% (1/14)	7% (1/14)	86% (12/14)	0

Background and purpose

Sentinel lymph node biopsy has been recommended for patients with invasive melanoma who do not have clinically detected nodal metastasis or distant metastasis because the procedure yields valuable prognostic information and is imperative for accurate staging of the disease. However, only a proportion of patients with SLN metastasis have additional non-SLN metastasis after undergoing CLND, whereas the efficacy of CLND for SLN-positive patients remains under debate. Anti-programmed cell death protein 1 (PD-1) antibodies and BRAF/MEK inhibitors have been approved as adjuvant therapies. These treatment options may also prolong the survival of patients with unresectable advanced melanoma. Recently, the results of several phase III RCT were published, in which the survival of patients with SLN metastasis in observation groups was compared with that of those in CLND groups.^{6,7} In this context, it was extremely important to examine which is the better choice for patients with SLN metastasis: observation or CLND.

Evidence

Three relevant RCT regarding CQ2 have been conducted to date.^{6,7,27} However, none of these three studies observed significantly prolonged melanoma-specific survival, RFS or distant metastasis-free survival. In one of these studies, lymphedema was found in 24.1% of the CLND group and 6.3% of the observation group ($P < 0.001$).⁶ A meta-analysis of these three studies revealed that no significant difference existed between the observation and CLND groups in terms of relapse-free survival (risk ratio, 0.65; 95% CI, 0.39–1.08; $P = 0.09$) or melanoma-specific survival (risk ratio, 0.95; 95% CI, 0.84–1.07; $P = 0.37$).

Comments

The primary outcome was an improvement in the OS or melanoma-specific survival. A meta-analysis of the three RCT (conferring a high level of reliability of evidence) failed to provide adequate evidence of a prolonged melanoma-specific survival period in the CLND group. On the other hand, most of the cases of SLN metastasis found in these studies were small in nature (e.g. <1 mm for the long diameter, detected only by polymerase chain reaction); this low tumor burden in SLN might have led to the absence of significant differences in the prognosis.^{1–3} Considering these points, the Japanese Melanoma Guidelines Committee could conclude that CLND should not be performed and, in fact, suggested not performing it.

Salient aspects for clinical application

Although the recommendation for pursuing CQ2 was 2 (weak, do not do it), this does not necessarily mean that CLND is contraindicated in all patients with SLN metastasis. The three RCT included in the aforementioned meta-analysis were from Western countries, where acral lentiginous melanoma, which accounts for approximately half of all melanomas in Japan, is very rare. Data from studies abroad can thus not necessarily be applied without caution to melanoma management in Japan. In addition, it is unclear as to whether follow-up ultrasound sonography in Japan is guaranteed to be of an equivalent quality to that performed in the observation groups in the studies. Some patients may request CLND in pursuit of a reduced possibility of any recurrence, even if they understand that CLND may not improve the OS. Therefore, treatment for patients with SLN metastasis should be carefully selected, with inclusion of CLND as a possible option, after appropriately conveying the message of CQ2 to patients.

Study subjects in the future

Further investigation is needed to elucidate whether CLND prolongs survival in patients with a high burden of melanoma tumor in SLN. As the included RCT suggest no significant survival benefit of CLND, it is doubtful that an additional RCT will be performed. If an RCT evaluating the significance of CLND is conducted in Japan, where the dominant clinical types of melanoma are different from those in the past RCT available from Western countries, such should provide a clearer answer to CQ2. This kind of study, however, would take a considerable amount of time to complete.

CQ3. Should additional iliac and obturator lymph node dissection (LND) be performed in patients who need inguinal LND?

Recommendation: Not to perform iliac and obturator LND is suggested as an additional procedure in patients who need inguinal LND.

Recommendation: 2

Evidence level: C

Agreement rate: 79% (11/14)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	21% (3/14)	0	79% (11/14)	0

Background and purpose

Sentinel lymph node biopsy has been routinely performed as a standard protocol of melanoma treatment. However, the indication of regional LND has been reconsidered recently.^{28,29} In Japan, acral melanoma of the foot is the most common clinical

type of melanoma observed, and we occasionally have the opportunity to perform inguinal LND (ILND). However, the addition of ipsilateral iliac and obturator LND (IOLND) has been controversial for a long time, and a standard indication for it remains unavailable.^{30,31} In cases where metastasis in inguinal lymph nodes or Cloquet's node is obvious, iliac and obturator lymph nodes are frequently involved.²⁸ The adoption of additional IOLND seemed to extend the survival period only minimally.^{28,32,33} It is important to clarify the benefit and indication of IOLND because the addition of IOLND to the treatment regimen increases surgical stress and postoperative complications.³⁴

Evidence

To elucidate any potential benefit from adding IOLND, we selected 10 reports,^{28–37} all of which were observational studies that compared the prognosis of patients who received ILND with or without IOLND. As a result of the meta-analysis of these 10 reports, there were no statistical differences in the RFS or OS between patients who underwent ILND plus IOLND or ILND alone, which was also true in each individual study (odds ratio, 1.00 [95% CI, 0.90–1.10; $P = 0.96$] for the RFS; and odds ratio, 1.06 [95% CI, 0.95–1.17; $P = 0.29$] for the OS). The rate of local recurrence tended to be lower in the ILND plus IOLND group, although not to a statistically significant degree. Regarding the rate of postoperative complications, there was no statistically significant difference between the two groups.

Comments

The latest NCCN guidelines (version 2, published in 2019)⁸ suggested that IOLND in addition to ILND should be performed if there is clinically obvious inguinal lymph node swelling, three or more involved inguinal lymph nodes, metastasis in Cloquet's node or radiological evidence of pelvic lymph node metastases. Another rationale for adding IOLND is the existence of pathological evidence of the extracapsular extension of tumor cells or a heavy nodal tumor burden.³² When there are inguinal lymph node metastases, pelvic lymph nodes are frequently involved. Therefore, some authors have suggested that ILND and IOLND should be performed simultaneously.³¹ Patients with pelvic lymph node metastasis, however, might already have disseminated hematogenous metastases, whose prognosis is very severe.²⁹ At this point, the pursuit of additional IOLND should be decided cautiously. A certain number of patients who received IOLND, however, survived for a long time after the operation, which supported the addition of this procedure to the treatment regimen.³⁸ Moreover, the existence of selection bias may explain the absence of significant difference in the OS between ILND plus IOLND and ILND alone because the surgeon might have decided to add IOLND in potentially severe cases.³¹ Even though there was no significant difference in the OS between the groups in the previous studies, IOLND might have improved the prognosis, which would have been worse than that in the control group.³¹ In the published work evaluated in this study, there was no report available suggesting that the addition of IOLND extended the RFS or OS in a statistically significant fashion.^{33,36,37} Even in our meta-analysis, no statistically significant difference was identified between the intervention and control

groups. On the other hand, adding IOLND did not increase the rate of postoperative complications, such as wound dehiscence, infection, lymphorrhea or lymphedema.³⁴ Some reports have suggested that IOLND decreased the rate of local recurrence.³⁷ Considering that the final purpose of regional LND is the prolonging of the RFS, however, the addition of IOLND cannot be justified only by a decrease in local recurrence. In cases with obvious metastasis in the pelvic lymph nodes on radiological imaging or in cases where multiple surgeries should be avoided due to poor general patient condition or advanced patient age, IOLND should be considered.

Salient aspects for clinical application

Across the evaluated studies in our meta-analysis, the status of inguinal metastasis was not identical. Some studies included clinically detected nodal metastasis, and others included clinically occult nodal metastases. Further, the quality of the intervention was varied among the studies because the indication of IOLND or the extent of LND was decided according to the surgeon's preferences in each study. The physician in charge should make a final decision as to whether IOLND should be performed or not in cases with obvious pelvic lymph node metastasis on imaging.

Study subjects in the future

To study the benefit of IOLND in Japanese melanoma patients, we need to conduct a multi-institutional study while avoiding bias in patient selection and the level of surgical intervention. Careful consideration of the design of this clinical trial is required because the results of the second international Multicenter Selective Lymphadenectomy Trial (MSLT-II) recently denied the benefit of early regional LND.⁶ In addition, immune checkpoint inhibitors or molecular-targeted agents have been applied as postoperative adjuvant therapies. With those evidences and specificity of Japanese melanoma patients, the indication of regional LND should be reconsidered even more carefully in the future.

CQ4. Should postoperative adjuvant radiotherapy be considered after regional LND for patients with stage III disease?

Recommendation: Postoperative adjuvant radiotherapy applied to the regional lymph node area following regional LND is suggested in patients with stage III disease when they have a high risk of regional recurrence.

Recommendation: 2

Evidence level: B

Agreement rate: 90% (9/10)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	90% (9/10)	0	10% (1/10)	0

Background and purpose

The observation of macroscopic regional lymph node metastases suggests a high risk not only of distant metastases but also of postoperative regional lymph node recurrences. Uncontrolled regional lymph node recurrences may deteriorate the patient's QOL with symptoms of bleeding, infection, pain and edema of the affected limb. Accordingly, interventions should be considered for postoperative patients at high risk of regional lymph node recurrences. On the other hand, the use of radiotherapy may cause complications, such as fibrosis or consolidation of the tissues and lymphedema of the limbs, although it is a major modality of postoperative intervention. This is why we performed a systematic review of the published work to elucidate the significance and appropriate parameters (e.g. radiation dose, clinical target volume) of postoperative radiotherapy for stage III patients.

Evidence

Three mentions of RCT were found concerning this CQ. Among these reports, only one³⁹ was selected for inclusion in the present systematic review because another report was a paper on the interim analysis of the same selected report,³⁹ and the third was an old study with a low-quality study design. The rate of regional lymph node recurrence was significantly lower in the postoperative adjuvant radiotherapy group (hazard ratio [HR], 0.52; 95% CI, 0.31–0.88). However, the RFS and OS were not prolonged by postoperative adjuvant radiotherapy (HR, 0.89 [95% CI, 0.65–1.22] for the RFS; and HR, 1.27 [95% CI, 0.89–1.79] for the OS). Concerning adverse events (AE), the difference in the rate of lymphedema was not significant between the adjuvant radiotherapy group and observation group, although the leg volume ratios were significantly higher in the former group. QOL satisfaction was lower in the postoperative adjuvant radiotherapy group at 12 months after randomization, but the difference was not significant at 60 months.

There were two prospective and 12 retrospective observational studies found in the published work; however, their results regarding rates of local control, progression-free survival (PFS), OS and AE were inconsistent. It was difficult to evaluate the significance of adjuvant radiotherapy after LND based on the results from the observational studies.

There was no interventional study evaluating the results of different dose-fractionation schedules between conventional fractionation (50–60 Gy/25–30 fractions/for 5–6 weeks) and hypofractionation (methods of a reduced number of the fraction by larger fraction size of ≥ 3 –4 Gy). The observational studies did not show significant variations in the recurrence rate between the different dose-fractionation schedules.⁴⁰

Comments

The systematic review revealed that the rate of regional lymph node recurrence was decreased by adjuvant radiotherapy following LND but that adjuvant radiotherapy was not associated with improved PFS or OS. Adjuvant radiotherapy may slightly deteriorate the QOL of the patients, but there was no clear evidence of a significant increase in the rate of AE. A decrease in the rate of regional lymph node recurrence by adjuvant

radiotherapy following LND was confirmed by the interventional study but was not supported by the results obtained from the observational studies. This may be caused by possible selection bias, in that high-risk cases might have been more prevalent in the adjuvant radiotherapy group.

Therefore, adjuvant radiotherapy following LND should be considered in patients at high risk of regional lymph node recurrences, such as those with clinically evident lymph node metastasis, multiple lymph node metastases and extranodal extension, with the aim of decreasing the risk of lymph node recurrence, although an improvement in the PFS or OS cannot be expected. This CQ targeted patients with a high risk of lymph node recurrence because the interventional study that we adopted in an attempt to answer this CQ included high-risk patients with clinically evident lymph node metastasis. This is why most panel members only weakly recommended pursuing adjuvant radiotherapy for stage III patients. On the other hand, the significance of adjuvant radiotherapy for patients with microscopic lymph node metastasis cannot be examined because there was no RCT on the subject of LND versus adjuvant radiotherapy for patients with positive SLN metastasis. Patients with stage III diseases have various levels of risk of lymph node recurrence. In addition, a clear survival benefit was not indicated even by the interventional study including only high-risk patients. Accordingly, some panel members suggested a “weak recommendation against intervention (adjuvant radiotherapy)”.

Salient aspects for clinical application

Patients must frequently visit their hospital or be hospitalized for certain periods of time in order to receive adjuvant radiotherapy. Accordingly, the need for adjuvant radiotherapy should be determined not only by the conditions of the tumor but also by the social circumstances and preferences of the patients, especially in the case of elderly patients who have difficulties in visiting the hospital every day. In addition, immune checkpoint inhibitors and molecular-targeted agents are approved for postoperative adjuvant chemotherapy by the Japanese health insurance system. Determining whether radiotherapy or these new agents are more appropriate in each individual case is difficult because no study has been conducted to date comparing these two modalities. Some panel members mentioned that adjuvant radiotherapy is useful, especially in those who have difficulty in receiving chemotherapy, such as patients with autoimmune diseases or without *BRAF* mutations.

Study subjects in the future

The study selected in this systematic review was conducted before the era of offering novel immune checkpoint inhibitors or molecular-targeted agents as adjuvant chemotherapy. In the days ahead, evidence should be gathered regarding the effectiveness of adjuvant radiotherapy not only as a single modality treatment but also as part of a multimodality treatment approach in combination with the use of these new agents. Moreover, indications for radiotherapy in future clinical trials may be completely different from those in previous studies because radiotherapy has been recognized to promote antitumor immunity.

CQ5. Should adjuvant systemic therapies be performed for patients with resected stage III or IV melanoma?

Recommendation: Adjuvant therapy with nivolumab for 1 year is recommended in patients with resected stage IIIB/C or IV melanoma (per the American Joint Committee on Cancer guidelines, 7th edition).

Recommendation: 1

Evidence level: A

Agreement rate: 83% (5/6)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
83% (5/6)	17% (1/6)	0	0	0

Recommendation: Adjuvant therapy with pembrolizumab for 1 year is recommended in patients with resected stage IIIA (diameter of >1 mm for SLN metastasis) to IIIC melanoma (per the American Joint Committee on Cancer guidelines, 7th edition).

Recommendation: 1

Evidence level: A

Agreement rate: 83% (5/6)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
83% (5/6)	17% (1/6)	0	0	0

Recommendation: Adjuvant therapy with a dabrafenib/trametinib combination for 1 year is recommended in patients with resected stage IIIA (diameter of >1 mm for SLN metastasis) to IIIC *BRAF*^{V600}-mutant melanoma (per the American Joint Committee on Cancer guidelines, 7th edition).

Recommendation: 1

Evidence level: A

Agreement rate: 100% (6/6)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
100% (6/6)	0	0	0	0

Recommendation: Adjuvant therapy with pegylated interferon (IFN)- α for up to 5 years is suggested in patients with resected stage III (per the American Joint Committee on Cancer guidelines, 6th edition) after the discussion regarding its associated toxicity and potential benefits.

Recommendation: 2
Evidence level: A
Agreement rate: 100% (6/6)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	100% (6/6)	0	0	0

Recommendation: Not to perform adjuvant therapy with ipilimumab (10 mg/kg; the dose is off-label in Japan) for up to 3 years is suggested in patients with resected stage IIIA (diameter of >1 mm for SLN metastasis) to IIIC melanoma (per the American Joint Committee on Cancer guidelines, 7th edition).

Recommendation: 2
Evidence level: A
Agreement rate: 100% (6/6)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	0	0	100% (6/6)	0

Background and purpose

Before the recent advances in systemic therapies for metastatic melanoma, IFN were the most frequently used agents in the adjuvant setting. Recently, systemic therapies with BRAF/MEK inhibitors, anti-cytotoxic T-lymphocyte-associated protein 4 antibody, or anti-PD-1 antibodies have exhibited their activities in the adjuvant setting. This systematic review aimed to evaluate the currently available adjuvant systemic therapies for patients with resected stage III or IV melanoma at a high risk of recurrence.

Evidence

Forty-one RCT covering the subject of adjuvant systemic therapies for melanoma were identified. The agents used in these trials included IFN- α /pegylated IFN- α in 20 RCT; immunotherapies other than IFN or immune checkpoint inhibitors in six RCT; chemotherapies other than dacarbazine (DTIC) in four RCT; DTIC in three RCT; ipilimumab, nivolumab,

pembrolizumab, a dabrafenib/trametinib combination or bevacizumab in one RCT each; and other agents in five RCT.

The EORTC18991 trial was a phase III RCT considering adjuvant therapy with pegylated IFN- α versus observation in patients with resected stage III melanoma. Pegylated IFN- α significantly prolonged the RFS (HR, 0.82; 95% CI, 0.71–0.96; $P = 0.01$) but did not improve the OS (HR, 0.98; 95% CI, 0.82–1.16; $P = 0.78$). Pegylated IFN- α was associated with significant toxicities: grade 3/4 AE occurred in 45% of the study participants, and 31% of the study participants discontinued treatment due to AE.^{41,42} Separately, the EORTC18071 trial, a phase III RCT evaluating adjuvant therapy with ipilimumab (10 mg/kg) versus placebo in patients with resected stage III cutaneous melanoma (stage IIIA melanoma with a tumor burden diameter of >1 mm within the SLN), revealed that significantly longer RFS (HR, 0.76; 95% CI, 0.64–0.89; $P < 0.001$) and OS (HR, 0.98; 95% CI, 0.82–1.16; $P = 0.78$) were achieved in the ipilimumab arm. However, adjuvant ipilimumab (10 mg/kg) was associated with a high frequency of toxicities; grade 3/4 AE occurred in 42% of the study participants and 52% discontinued treatment due to AE. Further, treatment-related deaths occurred in 1.1% of the study population: three patients died because of colitis, one patient died because of myocarditis and one patient died because of Guillain-Barré syndrome.^{43,44} The CheckMate 238 trial, in which patients with stage III disease (stage IIIA melanoma with a tumor burden diameter of >1 mm within the SLN) were assigned to either nivolumab (3 mg/kg) or ipilimumab (10 mg/kg), reported a significantly longer RFS in the nivolumab arm (HR, 0.65; 97.56% CI, 0.51–0.83; $P < 0.001$). Nivolumab had a more favorable toxicity profile, with grade 3/4 AE in 14% of the patients.² Nivolumab was approved as an adjuvant therapeutic option in Japan in July 2018. The EORTC1325/KEYNOTE-054 trial, where patients with stage III disease (stage IIIA melanoma with a tumor burden diameter of >1 mm within the SLN) were assigned to either pembrolizumab (200 mg/body) or placebo, revealed that a significantly longer RFS was achieved in the pembrolizumab arm (HR, 0.57; 98.4% CI, 0.43–0.74; $P < 0.001$). Grade 3/4 AE occurred in 14% of patients in the pembrolizumab arm.³ Pembrolizumab was approved as an adjuvant therapeutic option in Japan in December 2018. The COMBI-AD trial, in which patients with stage III disease (stage IIIA melanoma with a tumor burden diameter of >1 mm within the SLN) were assigned to receive either a dabrafenib/trametinib combination or placebo, revealed that a significantly longer RFS was achieved in the dabrafenib/trametinib combination arm (HR, 0.47; 95% CI, 0.39–0.58; $P < 0.001$).^{1,45} The dabrafenib/trametinib combination was approved as adjuvant therapy in Japan in July 2018. An interim analysis showed that the dabrafenib/trametinib combination tended to prolong the OS (HR, 0.57; 95% CI, 0.42–0.79; $P = 0.0006$), but this level of improvement did not meet the prespecified boundary of statistical significance at $P = 0.000019$.

Comments

The agents that have been proven to date to prolong RFS significantly include pegylated IFN- α , ipilimumab (10 mg/kg),

nivolumab (3 mg/kg), pembrolizumab (200 mg/body) and dabrafenib/trametinib combination. Conversely, the agent proven to significantly prolong the OS is ipilimumab (10 mg/kg); dabrafenib/trametinib combination therapy exhibited a tendency to prolong OS, whereas the effect of nivolumab or pembrolizumab on OS has not yet been reported. Although pegylated IFN- α was approved in Japan in May 2015 for use in patients with resected stage III melanoma after the completion of the Japanese phase I trial,⁴⁶ its recommendation was weak because it did not significantly improve OS. Also, while ipilimumab (10 mg/kg) significantly improved OS, it was not recommended because it exhibited an inferior level of efficacy and greater toxicity when compared with nivolumab. Nivolumab promoted a longer RFS than ipilimumab (10 mg/kg), which significantly prolonged OS as compared with the placebo, suggesting that nivolumab should prolong OS as well. Adjuvant treatment with nivolumab should be considered in patients with resected stage IIIB/C or IV melanoma. Pembrolizumab (200 mg/body) significantly improved RFS as compared with placebo, with a large amount of associated risk reduction (HR, 0.57). Thus, adjuvant treatment with pembrolizumab should be considered in patients with resected stage III melanoma. Dabrafenib/trametinib combination significantly improved RFS when compared with placebo, with a large degree of risk reduction (HR, 0.47); thus, adjuvant treatment with a dabrafenib/trametinib combination should be considered for patients with resected stage III *BRAF*^{V600E/K}-mutant melanoma.

Although Japanese institutions have participated in the COMBI-AD, CheckMate 238 and EORTC1325/KEYNOTE-054 trials, no RCT on the subject of adjuvant therapy conducted only in Japan have been completed. DAVFeron therapy, a combination of DTIC, nimustine and vincristine with local injection of IFN- β , which had been frequently used as adjuvant therapy for melanoma in Japan, was not assessed in these guidelines because DAVFeron therapy has never been evaluated in any prospective confirmatory trials. Adjuvant locoregional IFN- β was not assessed either because it is currently under evaluation in the RCT comparing it with surgery alone (Japan Clinical Oncology Group 1309, J-FERON).⁴⁷

Salient aspects for clinical application

For patients with resected melanoma, adjuvant therapy with nivolumab, pembrolizumab or dabrafenib/trametinib combination is currently available in Japan. In the pivotal RCT whose results led to the approval of these agents, most of the participants were patients with resected stage III (American Joint Committee on Cancer guidelines, 7th edition) cutaneous melanoma. In these trials, we need to recognize that the number of patients with acral melanoma was limited, a limited number of patients with mucosal melanoma were included only in the CheckMate 238 trial, and no patients with stage II melanoma were included. Moreover, we need to confirm the effects of nivolumab, pembrolizumab or dabrafenib/trametinib combination on OS.

Study subjects in the future

Adjuvant therapies designed based on the evidence for the treatment of non-acral cutaneous melanomas should be validated in patients with acral or mucosal melanoma. Adjuvant

therapy for patients with resected stage II melanoma should be established. There are no data available comparing dabrafenib/trametinib combination with nivolumab or pembrolizumab in patients with *BRAF*-mutant melanoma, and no robust data are available regarding the ideal treatment strategies for patients who develop recurrence after adjuvant treatment with these agents. Recently, some early-phase trials of neoadjuvant therapies with a small number of patients have suggested promising outcomes. However, the superiority of neoadjuvant approaches over adjuvant therapies has not yet been confirmed.

CQ6. Should there be periodic imaging tests performed in the follow-up period after curative resection?

Recommendation: The performance of periodic imaging tests during the follow-up period after curative resection is suggested.

Recommendation: 2

Evidence level: C

Agreement rate: 100% (10/10)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	100% (6/6)	0	0	0

Background, purpose

Because patients with melanoma are prone to experiencing recurrence and metastasis, following curative resection of the primary tumor or regional lymph nodes, affected individuals are typically monitored with periodic follow up. The main objective of these follow ups is the early detection of treatable recurrence or metastasis, but there is still no consensus as to the ideal frequency and timing for postoperative imaging. Clarifying what procedures to use for imaging tests, how frequently imaging should be done and when the patient should no longer undergo imaging is important following curative resection.

Evidence

There were only two studies that matched the inclusion criteria that directly compared survival between groups with or without periodic imaging tests.^{48,49} One of the studies contrasted patients with stages IB and IIA disease who periodically underwent or did not undergo ultrasonography, finding no significant difference between the two groups in terms of the patterns of progression, rates of metastasis or OS ($P = 0.44$).⁴⁸ Another study compared two groups of patients with stage IIA and IIB disease, respectively, who underwent at least 6 months of postoperative follow up. One group underwent at least two sessions of imaging, including chest radiography, whereas the other did not undergo any imaging during the follow-up period.

Ultimately, this study found no significant difference in the OS between the two groups ($P = 0.7527$).⁴⁹ Beyond these investigations, there were seven additional studies that indirectly compared the OS between patients whose recurrence of melanoma was discovered by periodic imaging and those whose recurrence was discovered during a physical examination conducted by themselves or by their doctors. Of these nine studies, four were non-randomized prospective observational studies and five were retrospective studies. None of the studies yielded evidence that periodic imaging tests have any significant effect on OS. In three studies, the duration of follow up was less than 1 year, whereas the analysis considering confounding factors, such as patient background and staging, was inadequate in eight of these studies.

Thus, there is no reliable evidence available in this regard, making it difficult to decide on a recommendation. It is impossible at this point to conclude that performing regular imaging tests across the board would prolong the OS in melanoma patients following curative resection.

Comments

Although there is no research showing that periodic imaging lengthened the OS, many other countries' guidelines recommend performing periodic imaging examinations following curative resection of melanoma.⁸ Therefore, under these current circumstances, it is very difficult to conduct an RCT investigating whether periodic imaging tests are appropriate or not. Moreover, prior to the advent of immune checkpoint inhibitors and molecular-targeted agents as novel drug options, there was no effective therapy capable of ensuring lengthy OS in advanced-stage melanoma patients, and early detection of recurrence or metastasis was thought not to have a good effect on prognosis. Novel pharmaceutical options are now available, making the early detection and early intervention of recurrence or metastasis to prolong OS feasible.^{50,51} Therefore, the Japanese Melanoma Guidelines Committee members agreed that "periodic imaging tests should be implemented during follow up after curative resection". Although specific details, such as the types, frequency and timing of imaging tests, vary across guidelines, the latest NCCN guidelines (version 2, published in 2019)⁸ recommend avoiding performing periodic imaging tests for melanoma *in situ* or in stages IA to IIA. Instead, they recommend the imaging tests to be done only when metastasis or recurrence is suspected. Further, in patients with disease stages IIB to IV, the latest NCCN guidelines recommend performing imaging tests every 3–12 months. They do not recommend periodic imaging tests to be conducted later than 3–5 years following surgery; imaging should be applied only when there are symptoms of metastasis or recurrence.

Salient aspects for clinical application

It is difficult to provide clear criteria for the frequency of imaging tests, which needs to be considered on a case-by-case basis. For computed tomography (CT) of the chest/pelvis and head, one session of imaging presented a radiation exposure dose of 15–20 and 85 mGy, respectively (diagnostic reference levels) in CTDI_{vol} (mean absorbed dose at each point on a phantom).⁵² With ¹⁸F-fluorodeoxyglucose (FDG) positron

emission tomography (PET) using FDG of 185 MBq, the effective dose (in terms of uniform irradiation of the whole body) is approximately 3.5 mSv.⁵³ According to the recommendations of the International Commission on Radiological Protection,⁵⁴ there is approximately a 5% extra lifetime mortality risk for radiation-induced cancer per 1 Sv (equivalent to 1 Gy in radiation used for diagnostic imaging) of whole-body irradiation. Thus, the benefits gained from imaging tests and the adverse effects associated with radiation exposure should both be taken into consideration when deciding to perform imaging. It is widely accepted that the mortality risk from radiation-induced cancer is not increased when a twice-annual CT or PET/CT regimen is continued for 5 years.

Study subjects in the future

With the advent of promising immune checkpoint inhibitors and molecular-targeted agents, the efficacy of performing periodic imaging assessments for the early detection of recurrence and metastasis must be additionally assessed in Japanese patients in the future.

CQ7. Are novel agents recommended for the treatment of MBM?

Recommendation: Several novel agents, including immune checkpoint inhibitors and molecular-targeted agents, are suggested for the treatment of MBM.

Recommendation: 2

Evidence level: C

Agreement rate: 90% (9/10)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
10% (1/10)	90% (9/10)	0	0	0

Background, purpose

Although novel agents, such as molecular-targeted agents and immune checkpoint inhibitors, have been recognized as first-line therapies for advanced melanoma, the efficacy of these agents on the OS for MBM is still unclear because the existing phase III clinical trials excluded patients with such. On the other hand, there have been several reports published evaluating the efficacy of these novel agents in patients with MBM. The purpose of this study was to evaluate the therapeutic effects of novel agents and conventional surgery and radiotherapy in patients with MBM.

Evidence

There were seven prospective studies and three retrospective studies available evaluating the efficacy of various kinds of treatment modalities for MBM. Among them, we selected five

phase II studies^{55–59} that evaluated OS, which is a primary outcome of this CQ. We also selected three additional studies to validate the clinical outcomes of local therapies (surgery and radiotherapy).^{60–62} A multicenter, open-label phase II trial for the assessment of the efficacy of vemurafenib for MBM reported that the median OS was 9.6 months (range, 0.7–34.3; interquartile range [IQR], 4.5–18.4) in patients who had received previous local therapy for MBM and 8.9 months (range, 0.6–34.5; IQR, 4.9–17.0) in those who had not.⁵⁵ According to a multicenter, open-label phase II trial (BREAK-MB), the median OS was 7.3 months (95% CI, 5.97–unreached) in *BRAF*^{V600E}-mutant melanoma patients who had received previous local therapy for MBM, 7.7 months (95% CI, 5.97–unreached) in *BRAF*^{V600E}-mutant melanoma patients who did not, 5.1 months (95% CI, 3.57–unreached) in *BRAF*^{V600K}-mutant melanoma patients with previous local therapy and 3.8 months (95% CI, 1.61–5.22) in *BRAF*^{V600K}-mutant melanoma patients without previous local therapy.⁵⁶

Another multicenter, open-label phase II trial that assessed the efficacy of dabrafenib/trametinib combination therapy (COMBI-MB) reported a median OS of 10.8 months (95% CI, 8.7–19.6) in cohort A (*BRAF*^{V600E}, asymptomatic MBM, no prior local therapy), 24.3 months (95% CI, 7.9–unreached) in cohort B (*BRAF*^{V600E}, asymptomatic MBM, prior local therapy), 10.1 months (95% CI, 4.6–17.6) in cohort C (*BRAF*^{V600D/K/R}, asymptomatic MBM, with or without prior local therapy) and 11.5 months (95% CI, 6.8–22.4) in cohort D (*BRAF*^{V600D/K/R}, symptomatic MBM, with or without prior local therapy).⁵⁷ On the other hand, the antineoplastic effects of immune checkpoint inhibitors were observed to be as follows: the median OS achieved with ipilimumab in patients with asymptomatic MBM was 7 months and that in those with symptomatic MBM was 4 months (no statistical analysis),⁵⁸ whereas the median OS achieved with nivolumab/ipilimumab combination therapy was unreached (median follow up, 14 months).⁵⁹ The 1-year survival rate for nivolumab/ipilimumab combination therapy among patients with asymptomatic MBM without previous local therapy was 81.5% (95% CI, 71.5–88.2). Because there were no similarities in PICO (i.e. P: patients, problem, population; I: interventions; C: comparisons, controls, comparators; O: outcomes) characteristics among these five selected studies as described above, we did not further conduct a meta-analysis for this CQ.

Comments

No phase III clinical trials have been completed that assessed the efficacy of novel agents or local therapies (e.g. surgery, radiotherapy) for MBM. Therefore, we instead selected several non-randomized phase II studies to estimate the efficacy of such novel agents. The median OS achieved for MBM was 1.7–2.1 months with palliative therapy, 2.5–5.1 months with radiotherapy, 5.5–8.7 months with surgery and 8.9–11.5 months with radiation with surgery.^{60–62} These previous data suggested that dabrafenib/trametinib combination therapy and nivolumab/ipilimumab combination therapy may prolong OS, although we could not compare the clinical studies directly. Notably, there are degrees of inconsistency and

inaccuracy of the estimated value of the OS within these selected studies due to selection bias and their small sample size. Therefore, the Japanese Melanoma Guidelines Committee members proposed a “conditional recommendation” for the intervention. Following the completion of several ongoing clinical trials to evaluate novel agents for MBM, the recommendation level for the present CQ can be revisited and may grow stronger in the future.

Salient aspects for clinical application

The evidence for the selection of appropriate therapy for MBM between novel agents and local therapies (i.e. surgery, radiotherapy) is still limited. Increasing numbers of studies have proven the efficacy of dabrafenib/trametinib combination therapy for *BRAF*^{V600E/K}-mutant melanoma and nivolumab/ipilimumab combination therapy for *BRAF* wild-type melanoma. Importantly, clinicians should take into account the age and performance status of patients and the AE of these protocols.

Study subjects in the future

Because there are several ongoing clinical studies evaluating the efficacy of novel agents in combination with local therapy for MBM abroad, similar studies could be reasonably initiated in Japan as well. To set up these clinical studies, the establishment of what constitutes local therapy (e.g. the time point for radiation, types of radiotherapy, stereotactic or whole-brain irradiation) is important. Establishing a high-quality randomized protocol of novel agents combined with surgery is difficult because the number of cases in which the surgical procedure in question is applicable may be very small. In the future, the development of a method to determine the ideal treatment for each patient based on several clinical factors (e.g. number of non-MBM cases, number of MBM cases, performance status, lactic acid dehydrogenase level) will be important.

CQ8. Which tumor samples of primary or metastatic melanoma should be chosen for appropriate genetic testing of *BRAF*^{V600} mutations?

Recommendation: Genetic testing for *BRAF*^{V600} mutations using metastatic tumor samples is suggested if metastatic tumor samples are available without highly invasive biopsies.

Recommendation: 2

Evidence level: B

Agreement rate: 100% (14/14)

Benefit with strong recommendation	Benefit with weak recommendation	Unable to determine recommendation	No benefit or risk with weak recommendation	No benefit or risk with strong recommendation
0	100% (14/14)	0	0	0

Background, purpose

Melanoma has certain driver mutations that mediate tumorigenesis and tumor growth. Small-molecule compounds that block aberrant signals mediated by $BRAF^{V600}$ mutations are effective in stage IV melanoma. While genetic testing for $BRAF^{V600}$ mutations can be performed using either primary or metastatic tissues, discordant results have been reportedly obtained. It is therefore important to choose an appropriate tissue (e.g. primary or metastatic tumor sample) for genetic testing of $BRAF^{V600}$ mutations because the outcome of the decision to apply BRAF/MEK inhibitors is critical in the prognosis of patients.

Evidence

There were 20 case-control studies identified in which $BRAF^{V600}$ mutation status was compared between primary and metastatic tumors derived from the same patients. The discordance rate of $BRAF^{V600}$ status was statistically analyzed using the DerSimonian-Laird method. As a result, the discordance between primary and metastatic tumors for $BRAF^{V600E}$ mutations was observed in approximately 13% of cases (95% CI, 0.08–0.18; $P < 0.01$). The probabilities for $BRAF^{V600E}$ -positive and $BRAF^{V600E}$ -negative statuses in metastatic tumors were 82% (95% CI, 0.71–0.94; $P < 0.01$) and 82% (95% CI, 0.70–0.94; $P < 0.01$) when the corresponding statuses in primary tumors were positive and negative, respectively. The level of publication bias assessed by funnel plot analysis was minimal. Detection bias attributed to differences in the methods of genetic testing and selection bias resulting from the enrollment of only patients with paired results from primary and metastatic tumors were observed. Additionally, indirectness due to differences in race and stage, imprecision due to differences in sample size, and high rates of heterogeneity ($I^2 = 70$ –80%) were observed in this meta-analysis.

Comments

We configured the discordance rate of $BRAF^{V600E}$ status between primary and metastatic tumors as a surrogate outcome because no cohort study has been conducted that investigated the effect of different tissues (i.e. primary vs metastatic tumors) used for genetic testing for $BRAF^{V600}$ status on response rates, PFS or OS. A previous meta-analysis that included 22 case-control studies reported the discordance rate as 13.3%, where $BRAF$ mutation status was compared between the primary and metastatic tumors derived from the same patients.⁶³ The current meta-analysis consisted of 20 eligible studies, which included 15 from a previous meta-analysis report.⁶³ The discordance rate in our meta-analysis was similar to that found in the previous report. In clinical settings, genetic testing using previously resected primary tumors typically determines the course of therapy and, therefore, we performed a meta-analysis regarding the probability of $BRAF^{V600E}$ mutation status in metastatic tumors by the status of primary tumors. The meta-analysis implied that approximately 20% of

the cases had a level of risk of incorrect decision-making. Taken together, we recommended performing genetic testing for $BRAF^{V600E}$ mutations using metastatic tumors, which are a real therapeutic target with BRAF/MEK inhibitors, provided that they are available without a highly invasive procedure.

Salient aspects for clinical application

In actual clinical settings, the highly invasive nature of metastatic tumor biopsy warrants the need to consider a biopsy of subcutaneous and superficial lymph node metastasis for examining the status of $BRAF^{V600}$ mutations. The decision should be made considering the general condition and preferences of the patient and the invasiveness of the procedure.

Study subjects in the future

The cohort studies included in the current meta-analysis showed findings of heterogeneity in race, methods used to detect $BRAF$ mutation and clinical stages of the tumors. The lack of cohort analysis comparing response rates, PFS and OS among the patients treated with BRAF/MEK inhibitors based on tissue samples used for genetic testing—either primary or metastatic tumors—warrants future prospective cohorts, including Japanese patients, to be additionally examined. Further analysis should incorporate methods of genetic testing approved by the Japanese health insurance system, performance status, prior therapies and clinical stages. While we considered only $BRAF^{V600E}$, novel small-molecule compounds targeting other genetic aberrations in melanoma may be developed in the near future. Therefore, similar analyses for each genetic aberration will be needed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Members of the Melanoma Guidelines Committee of the Japanese Skin Cancer Society

Table S2. Results of published work search with relevant key words in each clinical question