REVIEW

Received: November 2018
Accepted: January 2019

Comparison of Clinical Practice Guidelines for the Assessment and Management of Cutaneous Melanoma (Literature Review)

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BCCR
2019; 11(1):61-70
www.bccrjournal.com

ABSTRACT

Evidence shows that there has been an increasing incidence of melanoma cancer in Iran, especially among the young population, which has led to increased mortality, disability and disablement, mostly due to the complications of disease and treatment. New treatments such as targeted therapy are extremely costly, and their results are not clear.

The objective of this study is to review different current guidelines for the management of cutaneous melanoma cancer and discuss the differences in the various phases of patient assessment (prevention, risk factors, genetic assessment, clinical diagnosis, biopsy, staging, treatment and follow-up, pediatric melanoma, melanoma during pregnancy, and the necessity of social and mental support for melanoma patients). Then, based on the results, we will prepare a national guideline for the management of cutaneous melanoma in accordance with the prevailing conditions in Iran.

Keywords: Melanoma, Treatment, Prevention, Cancer

INTRODUCTION:

In recent years, there has been an increasing incidence of cutaneous melanoma in Iran , especially among the young population[1], which has led to increased mortality, disability and disablement, mostly due to the complications of disease and treatment. New treatments such as targeted therapy are extremely costly, and their results are not clear.

We aimed to apply one of the standard melanoma guidelines to the management of melanoma patients in Iran. However, after independent one-by-one review and assessment of the various guidelines, they were observed to be significantly different; therefore, we decided to design and establish a national guideline for the treatment of melanoma patients in Iran.

In this review study, we will discuss the differences between the eight standard guidelines listed below:

• **Guideline 1**: Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand:(update), 2008

• **Guideline 2**: Nova Scotia Cancer Care: Guidelines for the Management of Malignant Melanoma:(update), 2013

• **Guideline 3**: Guidelines of Care for the Management of Primary Cutaneous Melanoma (The American Academy of Dermatology), 2011

• **Guideline 4**: AHRQ: Agency for Healthcare Research and Quality, 2011

• **Guideline 5**: Cutaneous Melanoma: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up, 2015

• **Guideline 6**: Evidence-Based Clinical Practice Guideline: Treatment of Cutaneous Melanoma (American Society of Plastic Surgeons), 2007

• **Guideline 7**: NICE Guideline: Assessment and Management of Melanoma: (update), 2018

• **Guideline 8**: NCCN Guideline: Clinical Practice Guideline in Oncology Melanoma: (Update), 2018

PREVENTION AND RISK FACTORS:

Prevention of melanoma is only discussed in guideline-1[2], which may be due to the frequency of this type of disease in Australia. In total, four major points are mentioned in this guideline regarding melanoma prevention, as follows:

1. Protection of skin against UV rays, which are especially found in sunlight.
2. The best way to protect the skin from sunburn is by physical protection.
3. All different tanning methods are associated with an increased risk of melanoma.
4. Avoiding sunlight is associated with vitamin D deficiency in the body. Therefore, complete avoidance must be prohibited. Vitamin D supplements must be consumed in high-risk cases, where there is a need for complete sunlight avoidance.

Determining which persons are at risk of melanoma, or in other words, identifying high-risk persons who need clinical evaluation are important concerns in these guidelines. All guidelines agree that screening of the entire population has no economic justification. Another important issue agreed upon by all of these guidelines as requiring clinical evaluation is the presence of several moles on the body[2-9]. Guideline-2[3] claims that the risk of melanoma is two-fold in the presence of one dysplastic nevus, and the presence of more than 12 dysplastic nevi confers a 12-fold increased risk for melanoma. Regarding melanocytic nevi, it has been reported that a significant number of melanocytic nevi (more than 50) is a relative risk factor of 5-fold or greater for developing melanoma. Moreover, this guideline mentions some high-risk phenotypes and expresses that the blonde population with blue or green eyes and light or red hair and those who are more sensitive to sunlight and quickly become sunburned are more at risk of developing melanoma[3].

Personal and family history is considered important in all guidelines and is listed statistically in Guideline-2. A personal history of melanoma is associated with a 5-fold increased risk, whereas positive family history is accompanied by a 2-fold increased risk of the disease[3].
Regarding gender, guidelines 1 and 2 report that the male gender is more at risk of this cancer[2,3], and other guidelines have made no explicit claim[4-9].
In terms of different types of mole, Guideline-6 regards the presence of more than 30 normal moles or more than three atypical moles as a risk factor for melanoma[7].
Guidelines-2 and 5 recommend genetic assessment for high-risk patients; the BRAF mutation (a human gene that encodes a protein called "B-Raf") is reported to be associated with improper survival in both guidelines[3,6].
In terms of determining the need for genetic tests, all guidelines express the necessity of providing genetic counseling in specialized centers.
In high-risk persons, yearly specialized assessment has been suggested in Guideline -6. This assessment should be performed by a specialist familiar with melanoma, in order to identify colored lesions or suspicious moles[7].
Guideline-1 suggests that a complete skin examination, including photography or dermoscopy, be performed every 6 months. In addition, educating patients and their partners has been suggested in this guideline[2].
The clinical diagnosis of melanoma is based on the well-known ABCD abbreviation
A: Asymmetry,
B: Border irregularity,
C: Color variation or changes,
D: Diameter greater than 6mm,
E: Evolving is mentioned in guidelines-1, 2, and 5[2,3,6].
In Guideline-6, the letters E and F are defined as:
E. Evolutionary changes in color, size, symmetry, surface characteristics and symptoms, F. Funny-looking lesions[7].

In Guideline-2, it is suggested that the mentioned characteristics in the clinical diagnosis of melanoma be divided into a seven-item checklist consisting of three major and four minor characteristics[3], as presented below:

A) Major Characteristics

1. Change of size
2. Change of color
3. Change of shape

B) Minor Characteristics

4. Size greater than six mm
5. Change of sensation (e.g., itching)
6. Inflammation
7. Oozing, crusting or bleeding

BIOPSY

In all guidelines, it has been expressed that a biopsy must be carried out on suspicious lesions. In case of lack of biopsy, the lesions must be accurately followed up by dermoscopy or photography.
The correct method of excisional biopsy is explained in guidelines, as follows:

• Guidelines NCCN, Scotia, and American academy have reported the appropriate margin for biopsy of suspicious lesions to be between 1-3 mm[2,3,8].

• According to Guideline-1, a margin of 2 mm is sufficient.

In guidelines 1-4 and 6 and 8, an excisional biopsy must include the whole lesion and precede the next surgery. Application of other biopsy methods (e.g., punch or incisional) is not recommended unless the lesion has an extremely large size or the lesions are in sensitive areas such as the face.
The pathology must be reported by experienced pathologists in the area of pigmented lesions. The minimum items that must be reported include determining the thickness (Breslow), microscopic margins, mitotic rate, invasion rate (Clark), and presence or absence of

Table 1. Treatment is based on the thickness of lesion.

Tumor Thickness	Necessary Margin
in situ	0.5-1 cm
≤ 1 mm	1 cm
> 1-<2 mm	1-2 cm
> 2-<4 mm	2 cm
> 4 mm	2 cm

ulceration[2-5,9].

STAGING, TREATMENT AND FOLLOW UP

Staging of melanoma is based on the American Joint Committee on Cancer (AJCC) in all guidelines.

Treatment is based on the thickness of lesion (in guidelines-1, 2, 3, 5, 6, and 8), as presented in **Table1**:

• Stage 0 (in situ) and IA (thickness <0.8 mm [T1a] and no ulceration)

According to all guidelines, in this stage history taking and clinical examination are sufficient and there is no need for any special laboratory tests.

In Guideline-2, it is expressed that there is no need for paraclinical measures at this stage if there are no signs or symptoms of distant disease. This is mainly due to the fact that these measures (e.g., CT scans, CXR or bone scan), only increase the chance of false positive cases and there is a very low probability of the discovery of occult metastasis.

In Guideline-8 (NCCN), it is asserted that there is no need for the evaluation of lymph nodes via radiological methods. However, a biopsy must be performed if lymph nodes are clinically stimulated and negative ultrasound is unable to replace biopsy at this stage. Any abnormal findings in ultrasound should be confirmed by biopsy.

• Stage IB

Ulceration + ([T1a] 0<0.8 mm)

Ulceration ± ([T1b] 0.8-10 mm)

The main treatment at this stage includes wide location excision (WLE) in all guidelines.

The IA&IB stage may be the most questionable stage in terms of the evaluation of lymph nodes. The need to perform a SLNB at this stage varies in different guidelines.

In Guideline- 8 (NCCN), it is expressed that if the risk of lymph involvement is 5-10%, sentinel lymph node biopsy (SLNB) can be performed, which is mostly observed in the IB stage. However, if T1a (Breslow thickness lower than 0.8 mm) is established , it is better to conduct SLNB if we witness an adverse feature in pathology, such as a mitotic rate above 2 mm^2; especially in younger individuals, or in the presence of lymphatic or vascular invasion. According to NCCN, while SLNB is an important tool for staging, it has no impact on survival[9].

Referring to several studies, Guideline-2 expresses that SLNB must be used in T1b as a staging tool[3]. On the other hand, Guideline-3 mentions that SLNB is not required for a thickness below 0.75 mm, However, this procedure is recommended for thicknesses above 1 mm[3]. In thicknesses below 0.75 mm, this method can be discussed with the patient if there are any adverse features. The same has been expressed in guidelines-4, 5, and 7.

• Stage II

It has been expressed in all guidelines that history

taking and clinical examination are sufficient at this stage, and there is no need for laboratory or radiological tests. Treatment at this stage is WLE, and SLNB is suggested for cases with a thickness greater than 1 mm by guidelines-3 and 4 and greater than 0.75 mm by Guideline-5. Other guidelines recommend the use of SLNB for these patients.

In terms of evaluation of distant metastasis in stage II or lower, different guidelines do not recommend assessment if there is no clinical evidence of metastasis. However, some guidelines suggest the evaluation of metastasis in patients with positive SLNB. According to Guideline- 8 (NCCN), imaging for staging with a 2B level of evidence (**Supplement Table 1**) is possible in case of positive SLNB; However, in all cases where there are symptoms and signs in favor of metastasis, full imaging evaluations must be carried out[8].

According to Guideline-1, in melanoma cases with a thickness greater than 1 mm, a complete discussion must be held with the patient and their companions regarding the recommendation of SLNB; this procedure should be carried out for better staging and determination of prognosis. Based on this guideline, SLNB should only be performed in centers that have proper access to experienced surgeons in the fields of cancer, nuclear medicine, and experienced pathologists.

In Guideline-7, it is expressed that the advantages and disadvantages of the procedure must be explained (both in writing and verbal) to patients before complete dissection of the regional lymph node in stage III patients.

Guideline-1 expressed that lymph node dissection should be recommended to all cases with evidence of lymphatic involvement and no distant metastasis. However, this procedure is only possible in experienced cancer centers.

• Stage III

In this stage, the main issue of guidelines is performing lymph node dissection based on the presence or lack of clinical evidence and imaging indicative of metastasis. Imaging is performed based on specific symptoms and signs and as a baseline staging procedure. At this stage, treatments of choice are WLE and therapeutic lymph node dissection. According to Guideline- 8 (NCCN), various forms of biopsy (e.g., fine needle aspiration [FNA], core needle biopsy (CNB), or excisional or incisional biopsy) must be performed in cases of clinically positive lymph nodes[9].

Guideline-1 expressed that distant metastasis must be carefully excluded before recommending therapeutic dissection[2].

In Guideline-2, complete dissection is recommended

Supplement Table 1:NCCN Categories of Evidence and Consensus

Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based on lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based on lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based on any level evidence, there is major NCCN disagreement that the intervention is appropriate.
All recommendations are category 2A unless otherwise noted.

in patients with cytologically or histologically proved regional nodal metastases. Of course, the development of palpable lymph node metastases is significantly correlated with substantially diminished survival in all cases (10% to 50%). This guideline emphasizes that regional lymph node dissection (L.N.D) should not be performed routinely in patients with bulky and matted lymph node metastasis, since the prognosis is very poor and it is better to perform palliative treatment by various radiotherapy methods[3].

In Guideline-6, lymph node dissection is recommended in three cases:

1. Positive SLNB reported in pathology
2. Presence of clinically positive lymph nodes (even if involvement is detected in several basins)
3. As a form of palliation in distant metastasis

Guideline-7 recommends performing dissection on patients in case of positive SLNB or lymphatic involvement in the clinic only after a complete explanation of its advantages and disadvantages to the patient, in both written and verbal form. In the end, this guideline mentions that lymph node dissection should be considered in all stage IIIB and IIIC cases or cases with metastatic lymph node detected via imaging.

• Stage III (In-transit or Satellite Metastasis)

According to Guideline-8 (NCCN), the pathology of patients must be confirmed in this stage by FNA, CNB, excisional or incisional biopsy. Complete imaging and full evaluation of metastasis must be carried out for staging of the disease. A multi-disciplinary team (MDT) should convene, and a proper collective decision must be made for the treatment of these patients. Guideline-2 recommends performing PET/CT scan for these patients, if possible. It also mentions compulsory evaluation of lactic dehydrogenase (LDH) if recurrence is observed in the lymph nodes; however, this evaluation is optional in other cases. There is no standard method of treatment in this stage, and the MDT should make the final decision. It is also expressed in this guideline that melanoma is curable in one-third of cases that present with in-transit or local melanoma, or with lymphatic recurrence , and that patients must remain optimistic regarding treatment[3].

In Guideline-5, it has been declared that surgery or radiotherapy can be performed if there is limited in-transit metastasis. In case of wide-spread metastasis (involvement of more than five different locations) systematic therapy, limb perfusion, radiotherapy, Talimogene laherparepvec (T-VEC) or electrochemotherapy can be carried out as treatment methods. In all cases, the patient's condition should be discussed with the MDT and all decisions must be made in valid cancer centers[6].

In addition, Guideline-7 emphasizes referral of these patients to MDTs in valid cancer centers.

Stage IV

According to Guideline-8 (NCCN), a biopsy is required at this stage to confirm the diagnosis if clinically indicated. This guideline suggests FNA, core, incisional, or excisional biopsy to detect metastasis. In this stage, CBC, LDH is measured in all patients. In addition, BRAF and KIT (this gene encodes the human homolog of the proto-oncogene c-kit) mutational analyses should be performed on biopsy samples (for targeted therapy). According to the mentioned guideline, decisions regarding the treatment of these patients must be made by the MDT. Surgery or systematic treatments can be suggested if the disease is limited or resectable and in disseminated (unresectable) cases based on the presence or lack of presence of brain metastasis[9].

Similarly, surgery is recommended for operable metastases in Guideline-1. Regarding brain metastasis, both surgery and stereotactic methods are suggested in the aforementioned guideline[2].

In Guideline-2, clinical trial treatment (with temozolomide or dacarbazine and treatment with cisplatin or daclitaxell as the second line) is recommended for

non-resectable cases. Regarding bone metastases, radiotherapy is suggested. It is expressed that IL2 has yielded a complete clinical response of up to 5% in other countries. However, there is no access to IL2 in countries included in this guideline. On the other hand, new systematic treatments are suggested for metastatic melanoma in the mentioned guideline[3]. In patients with BRAF mutation, vemurafenib can be the first line of treatment. However, dacarbazine is recommended as the first line of treatment in cases with no BRAF mutation. The second line of treatment for patients with a proper clinical condition is ipilimumab, which regulates the immune system[3].

In Guideline-5, the decision regarding the treatment of metastatic melanoma depends on the BRAF gene (V600). Approximately one-half of advanced (unresectable or metastatic) melanomas harbor a mutation in the BRAF gene, with V600E being the most common mutation[10]. According to this guideline, it is better to assess this gene in the metastasis sample. Nonetheless, the mutation can be evaluated in the primary tumor if it is not possible to take samples from the metastasis at this stage. The first and second treatment lines include anti-PDL1 (e.g., Pembrolizumab, Nivolumab, and Ipilimumab) and anti-CTLA4 antibodies. The BRAF/MEL inhibitors are recommended for patients with a BRAF mutation. It may be possible to prescribe cytotoxic drugs (e.g., Termozolomide and Dacarbazine [DTIC]) in case of lack of access to targeted therapy compounds[6].

The topic of systematic treatments is not covered in Guideline-6 and patients are referred to oncologists to receive care at this stage.

In Guideline-7, metastatic patients are referred to experienced centers for MDT decision-making. However, surgery is acceptable, if possible. Regarding systematic treatments, the following drugs are mentioned[8]:

- **Debrafenib**: for metastatic or non-resectable cases with a BRAF mutation (V600)
- **Dacarbazine**: used in stage IV in the event that there is no proper targeted therapy or immunotherapy.
- **Ipilimumab**: first or second line treatment in stage IV, which is non-resectable.
- **Vemurafenib**: recommended for non-resectable cases or cases with metastatic melanoma with a BRAF mutation (V600).

In terms of systematic treatments in metastatic or non-resectable cases, Guideline-8 (NCCN) expresses the following items: The first line of treatment includes immunotherapy. In case of a BRAF mutation (V600), targeted therapy is suggested, especially if there is a need for quick response to treatment. The second line of treatment includes monotherapy with anti-PD-1, high-dose IL-2, or Imatinib (in case of KIT mutation) if disease progression is detected despite the first line of treatment or if there is a need for maximum clinical response to BRAF targeted therapy[9].

RADIOTHERAPY:

In terms of radiotherapy in melanoma, it could be said that the best conclusion is expressed in Guideline-8 (NCCN). In the initial treatment, radiotherapy is performed as an adjuvant treatment for the following cases:

1. Close margin, when re-resection is not possible.
2. Different types of deep desmoplastic melanoma with a close margin, when re-resection is not possible, either with or without the presence of wide neurotropism.

In cases of regional disease, radiotherapy is considered as an adjuvant or palliative treatment. Adjuvant treatment can be used for the following cases (CAT2B) (**Supplement Table 1**):

Presence of extranodal invasion, or:

1. In the face (parotid gland), if >1 lymph nodes with any size are involved.
2. In the neck: >2 lymph nodes and/or >3 cm tumor in lymph nodes
3. Axillary: 2≤ lymph nodes and/or >3 cm tumor in

lymph nodes
4. Inguinal: 3≤ lymph nodes and/or 4≤ cm tumor in lymph nodes

Radiation can be considered as a palliative or definitive treatment in patients with unresectable in-transit, satellite, or nodal involvement. This guideline also mentions use of radiotherapy in residual local, satellite, or in-transit disease after initial treatment[9].

FOLLOW-UP:

Post-treatment care has been considered in various guidelines. The common point in all of these guidelines is the key role of health education. The skin self-examination method, and in some guidelines, self-examination of lymph nodes are extremely important, as mentioned below. In Guideline-8 (NCCN), the general follow-up notes at all stages include skin and lymph node examination. In stage 0, blood and radiological tests are not recommended. Radiological examination is only necessary in some cases when there are positive notes in the history and clinical examination[9].

In guidelines 1, 2, 3, 5, 6, and NCCN, follow-up in Stage 0 (in situ) and IA includes annual total skin self-examination (according to NCCN, this examination includes skin and important lymphatic areas). The NCCN recommends that if the results of lymphatic examination are not clear, then ultrasound must be carried out at intervals of 3-12 months for a duration of two to three years. In stage IIA or lower, patients are encouraged to refer to specialists every 6-12 months for five years, and annually after that. In stages IIB to IV, referral should occur every three to six months for the first two years, and then every 3-12 months for three years, and annually after that. In addition, imaging is based on the symptoms and signs of the disease at all stages of the disease. In more advanced stages, routine imaging is CAT2B (**Supplement Table 1**). However, no routine imaging method is recommended after three-five years, regardless of disease stage. In Guideline-1, it is expressed that the time of referral to the doctor may vary depending on the opinion of specialists and the condition of the patient. In stage I, a referral should occur every six months to five years. In more advanced stages, a referral is required every three-four months for five years, and then annually after that[2].

More accurate numbers are stated in Guideline-2. In the first three years, a referral is required every three-six months (in stage I) and every three months (in stages II and III). In the next two years, a referral is needed every six months, and then annually after that. In stage IV, referral must be carried out every three months depending on the opinion of specialists. In this guideline, routine laboratory or imaging methods are not recommended[3].

In Guideline-5, health education recommendations are explained in detail. Generally, sun protection and avoidance of any solar or artificial UV waves is mentioned. It is explicitly stated in this guideline that there is no definitive way to summarize the time of referral to a specialist, and it cannot be conclusively decided as to which paraclinical method is most useful. Ultrasound of lymph nodes, CT or PET/CT may aid in early detection of recurrence and metastasis in high-risk patients (thick or metastatic melanoma). Contrary to other guidelines, a point is made about laboratory tests in this guideline, namely the fact that increased serum level (S-100) is more useful in the diagnosis of advanced disease, compared to LDH[6].

In Guideline- 6, it is expressed that referral intervals depend on the stage of the disease. In addition, paraclinical assessment is based on the opinion of the specialist. In patients with no signs of disease, most diagnostic tests have no special value. This guideline refers to melanoma in children in this section, stating that while lymphatic involvement is more common in children, the possibility of its recurrence is lower in these individuals[7].

Various referral intervals are considered in Guideline-7

based on the condition of the patient. However, an important note in this guideline is attention to vitamin D deficiency in patients and a strong recommendation to quit smoking (whether active or passive)[8]. In terms of imaging in stages IIC and III, it is expressed that sufficient written and verbal explanation must be provided to patients (regarding the advantages and disadvantages of the process) prior to initiation of the procedure. According to this guideline, performing various paraclinical methods exposes patients to abundant X-rays and makes them nervous. For instance, it is expressed that the risk of cataracts increases following continuous scanning of the neck and brain. Scanning increases the probability of thyroid cancer. In all cases, false positive cases lead to anxiety in patients[8].

MELANOMA IN CHILDREN:

Only guidelines-1 and 6 briefly mention pediatric melanoma, both regarding its better prognosis in infants[2,7].

MELANOMA DURING PREGNANCY:

This issue is covered in guidelines-1 and 2. In the former, it is expressed that any changes in colored spots and moles during pregnancy should be taken seriously. While treatment is similar to non-pregnant cases, the only difference is that SLNB is performed with Technetium[2].

In Guideline-2, it is stated that melanoma during pregnancy may lead to metastasis to the fetus and the placenta. In addition, there is a possibility of increased color of lesions during pregnancy due to hormonal changes. Moreover, melanoma has a more invasive behavior in pregnancy.75-90% of cases of melanoma recurrence occur during the first two to three years. Therefore, it is better to refrain from pregnancy during these years. It is notable that biopsy must be performed on all suspicious colored lesions during pregnancy. In case the lesion is thicker than 1 mm with no clinical evidence of lymph node involvement, SLNB can be performed with Technetium or Vita Blue Dye. Nonetheless, the safety of these methods during pregnancy is not definitive. In addition, since L.N.D in melanoma does not improve survival rate, it can be performed in pregnant individuals[3].

THE NECESSITY OF SOCIAL AND MENTAL SUPPORT FOR MELANOMA PATIENTS:

This issue is mostly covered in guidelines- 1 and 2. In the former, it is expressed that support structures are required to improve the quality of life of these patients. In addition, personnel dealing with these patients must receive necessary education as well[2].

In Guideline 2, it is affirmed that while all cancer patients need support, more requirements might be observed in the groups presented below:

1. Patients with unfavorable health status
2. Patients with unfavorable coping ability
3. Patients with no social media networks

In this guideline, it is expressed that 30% of melanoma patients have some level of depression, anxiety and adjustment difficulties at the time of diagnosis and treatment.

It is notable that in addition to patients, family members and relatives should be provided with support as well[3].

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