

Immunosuppression

The strong association between immunosuppression and MCC is well known^{10,34,35} (AJCC Level of Evidence: I). Whether compromised immune surveillance is the result of an underlying comorbidity, such as chronic lymphocytic leukemia, or immunosuppressive medication to prevent organ rejection, it increases the risk of developing MCC and negatively influences the subsequent immune response against the tumor, resulting in a higher mortality rate. Similarly, immune senescence, the natural decline of the immune system with age, is believed to be a contributing factor in the continually increasing incidence of MCC with advancing age.³⁶ Because of the subjective nature of this known prognostic factor, immunosuppression is not incorporated in the staging system. However, the practitioner is strongly encouraged to maintain a higher level of suspicion for the development of MCC in an immunocompromised patient, and to bear in mind the more aggressive course of MCC in the context of suppressed immune status when considering treatment options and surveillance for such patients.³⁷

RISK ASSESSMENT MODELS

The AJCC recently established guidelines that will be used to evaluate published statistical prediction models for the purpose of granting endorsement for clinical use.³⁸ Although this is a monumental step toward the goal of precision medicine, this work was published only very recently. Therefore, the existing models that have been published or may be in clinical use have not yet been evaluated for this cancer site by the Precision Medicine Core of the AJCC. In the future, the statistical prediction models for this cancer site will be evaluated, and those that meet all AJCC criteria will be endorsed.

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed (e.g., curetted)
T0	No evidence of primary tumor
Tis	<i>In situ</i> primary tumor
T1	Maximum clinical tumor diameter ≤2 cm
T2	Maximum clinical tumor diameter >2 but ≤5 cm
T3	Maximum clinical tumor diameter >5 cm
T4	Primary tumor invades fascia, muscle, cartilage, or bone

Definition of Regional Lymph Node (N)

Clinical (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be clinically assessed (e.g., previously removed for another reason, or because of body habitus)
N0	No regional lymph node metastasis detected on clinical and/or radiologic examination
N1	Metastasis in regional lymph node(s)
N2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) <i>without</i> lymph node metastasis
N3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) <i>with</i> lymph node metastasis

Pathological (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed (e.g., previously removed for another reason or <i>not</i> removed for pathological evaluation)
pN0	No regional lymph node metastasis detected on pathological evaluation
pN1	Metastasis in regional lymph node(s)
pN1a(sn)	Clinically occult regional lymph node metastasis identified only by sentinel lymph node biopsy
pN1a	Clinically occult regional lymph node metastasis following lymph node dissection
pN1b	Clinically and/or radiologically detected regional lymph node metastasis, microscopically confirmed
pN2	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) <i>without</i> lymph node metastasis
pN3	In-transit metastasis (discontinuous from primary tumor; located between primary tumor and draining regional nodal basin, or distal to the primary tumor) <i>with</i> lymph node metastasis

Definition of Distant Metastasis (M)

Clinical (M)

M Category	M Criteria
M0	No distant metastasis detected on clinical and/or radiologic examination
M1	Distant metastasis detected on clinical and/or radiologic examination
M1a	Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s)
M1b	Metastasis to lung
M1c	Metastasis to all other visceral sites

Pathological (M)

M Category	M Criteria
M0	No distant metastasis detected on clinical and/or radiologic examination
pM1	Distant metastasis microscopically confirmed
pM1a	Metastasis to distant skin, distant subcutaneous tissue, or distant lymph node(s), microscopically confirmed
pM1b	Metastasis to lung, microscopically confirmed
pM1c	Metastasis to all other distant sites, microscopically confirmed

AJCC PROGNOSTIC STAGE GROUPS

Clinical Stage Group (cTNM)

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2-3	N0	M0	IIA
T4	N0	M0	IIB
T0-4	N1-3	M0	III
T0-4	Any N	M1	IV

Pathological Stage Group (pTNM)

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2-3	N0	M0	IIA
T4	N0	M0	IIB
T1-4	N1a(sn) or N1a	M0	IIIA
T0	N1b	M0	IIIA
T1-4	N1b-3	M0	IIIB
T0-4	Any N	M1	IV

REGISTRY DATA COLLECTION VARIABLES

- 1. Largest tumor diameter (in millimeters, measured clinically, or histologically if not available)
- 2. Regional nodal status (examined clinically, pathologically, or neither)

- 3. Unknown primary status (yes/no)
- 4. Tumor thickness (whole millimeters)
- 5. Excision margin status (tumor base transected or not transected)
- 6. Profound immunosuppression (no immunosuppressive conditions, HIV/AIDS, solid organ transplant recipient, chronic lymphocytic leukemia, non-Hodgkin lymphoma, multiple conditions, condition NOS)
- 7. LVI (present/absent/no comment by pathologist)
- 8. MCPyV-positive staining by IHC (yes/no/not applicable)
- 9. p63-positive staining by IHC (if applicable) (yes/no)
- 10. Tumor-infiltrating lymphocytes in primary tumor (not present; present, nonbrisk; present, brisk; present, NOS)
- 11. Growth pattern of primary tumor (circumscribed/nodular or infiltrative)
- 12. Extranodal extension in regional lymph node(s) (yes/no)
- 13. Tumor nest size in regional lymph node(s) (greatest dimension of largest aggregate in millimeters)
- 14. Isolated tumor cells in regional lymph node(s) (yes/no)
- 15. Eyelid tumor involving the upper or lower eyelid, or both
- 16. Eyelid tumor involving the eyelid margin, defined as the juncture of eyelid skin and tarsal plate at the lash line; if present, is the eyelid margin involvement full thickness? (no/yes, no full thickness/yes full thickness)

HISTOLOGIC GRADE (G)

There is no recommended histologic grading system at this time.

HISTOPATHOLOGIC TYPE

Although several distinct morphologic patterns have been described for MCC, none has been reproducibly found to be of prognostic significance. These histologic subtypes include intermediate type (most common), small cell type (second most common), and trabecular type (least common but most characteristic pattern of MCC).²³