Protocol for the Examination of Specimens from Patients with Diffuse Pleural Mesothelioma

Version: 5.0.0.0
Protocol Posting Date: December 2024
CAP Laboratory Accreditation Program Protocol Required Use Date: September 2025
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes extrapleural pneumonectomy, pleurectomy, and decortication procedures
Tumor Type	**Description**
Diffuse pleural mesothelioma#	

 # Localized pleural mesothelioma can be reported using this protocol although pTNM pathologic stage classification is not applicable.

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens

The following tumor types should NOT be reported using this protocol:

Tumor Type
Solitary fibrous tumor
Peritoneal mesothelioma
Lymphoma (consider the Precursor and Mature Lymphoid Malignancies protocol)
Sarcoma (consider the Soft Tissue protocol)

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Glossary:
Author: Expert who is a current member of the Cancer Committee, or an expert designated by the chair of the Cancer Committee.
Expert Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements

Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.

A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.

**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 5.0.0.0

- Cover page update, including title change
- Version 9 pTNM Classification update
- Updates to content and explanatory notes, to incorporate pTNM updates to AJCC Version 9

Reporting Template
Protocol Posting Date: December 2024
Select a single response unless otherwise indicated.
CASE SUMMARY: (DIFFUSE PLEURAL MESOTHELIOMA)
Standard(s): AJCC 9

CLINICAL

+Clinical History (select all that apply)
___ Neoadjuvant therapy performed (specify type, if known): _____
___ Other (specify): _____

SPECIMEN (Note A)

Procedure (select all that apply)
___ Extrapleural pneumonectomy
___ Extended pleurectomy / decortication
___ Pleurectomy / decortication
___ Partial pleurectomy
___ Other (specify): _____
___ Not specified

Specimen Laterality
___ Right
___ Left
___ Not specified

TUMOR

Tumor Focality (Note B)
___ Localized
___ Diffuse
___ Cannot be determined: _____

Tumor Site (select all that apply)
___ Parietal pleura: _____
___ Visceral pleura: _____
___ Diaphragm: _____
___ Other (specify): _____
___ Not specified

+Tumor Size (for localized tumors only)
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm
___ Cannot be determined (explain): _____

Histologic Type (Note C)

___ Epithelioid mesothelioma

+Architectural Pattern (percentages must total 100%) (select all that apply)

___ Tubulopapillary: _____ %
___ Trabecular: _____ %
___ Adenomatoid: _____ %
___ Solid: _____ %
___ Micropapillary: _____ %
___ Other (specify): _____

+Cytological Features (select all that apply)

___ Rhabdoid
___ Deciduoid
___ Small cell
___ Clear cell
___ Signet ring
___ Lymphohistiocytoid
___ Pleomorphic
___ Other (specify): _____

+Stromal Features (select all that apply)

___ Myxoid predominant
___ Other (specify): _____

___ Sarcomatoid mesothelioma

+Cytological Features (select all that apply)

___ Lymphohistiocytoid
___ Transitional
___ Pleomorphic
___ Other (specify): _____

+Stromal Features (select all that apply)

___ Desmoplastic
___ With heterologous differentiation
___ Other (specify): _____

___ Biphasic mesothelioma

Percentage of Sarcomatoid Pattern

___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined

___ Other histologic type not listed (specify): _____
___ Cannot be determined (explain): _____

+Histologic Type Comment: _____

+Nuclear Atypia Score#

 # Used to determine histologic grade of epithelioid mesothelioma

___ 1 (mild)
___ 2 (moderate)
___ 3 (severe)

___ Cannot be determined: _____

+Mitotic Count Score#
 # Used to determine histologic grade of epithelioid mesothelioma
___ 1 (low, up to 1 mitosis per 2 mm2)
___ 2 (intermediate, 2 to 4 mitoses per 2 mm2)
___ 3 (high, 5 or more mitoses per 2 mm2)
___ Cannot be determined: _____

+Nuclear Grade# (sum of nuclear atypia and mitotic count scores)
 # Used to determine histologic grade of epithelioid mesothelioma
___ 1 (sum score of 2 or 3)
___ 2 (sum score of 4 or 5)
___ 3 (sum score of 6)
___ Cannot be determined: _____

+Necrosis
___ Not identified
___ Present
___ Cannot be determined: _____

Histologic Grade (Note D)
___ Low grade (nuclear grades 1 and 2 without necrosis)
___ High grade (nuclear grade 2 with necrosis, or nuclear grade 3 with or without necrosis)
___ Cannot be determined: _____

Tumor Extent (Note E) (select all that apply)
___ Limited to parietal pleura without involvement of ipsilateral visceral, mediastinal, or diaphragmatic pleura
___ Limited to parietal pleura with focal involvement of ipsilateral visceral, mediastinal, or diaphragmatic pleura
___ All ipsilateral pleural surfaces (including fissure)
___ Diaphragmatic muscle
___ Lung parenchyma
___ Endothoracic fascia
___ Mediastinal fat
___ Soft tissues of chest wall in a solitary focus
___ Soft tissues of chest wall diffusely or in multiple foci
___ Into but not through the pericardium
___ Rib(s)
___ Mediastinal organ(s) (specify): _____
___ Other (specify): _____
___ Cannot be determined: _____
___ No evidence of primary tumor

Treatment Effect (Note F)
___ No known presurgical therapy
___ Not identified
___ Present
Percentage of Residual Viable Tumor
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note G)

Margin Status
___ All margins negative for mesothelioma
___ Mesothelioma present at margin
Margin(s) Involved by Mesothelioma
___ Specify involved margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Nodal Site(s) with Tumor (select all that apply)
___ Bronchopulmonary: _____
___ Hilar: _____
___ Ipsilateral mediastinal (including internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal nodes): _____
___ Contralateral mediastinal (including internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal nodes): _____
___ Supraclavicular: _____
___ Other (specify): _____
___ Cannot be determined: _____
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Non-regional lymph node(s): _____
___ Other (specify): _____
___ Cannot be determined: _____

pTNM CLASSIFICATION (AJCC Version 9)# (Note H)
 # TNM descriptors are applicable only to diffuse pleural mesothelioma.
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
___ pT not assigned (localized pleural mesothelioma)
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pT1: Tumor limited to the ipsilateral pleura with no involvement of the fissure
___ pT2: Tumor involving the ipsilateral pleura and with any of the following: Involvement of the fissure; or Ipsilateral lung parenchyma invasion; or Diaphragm (non-transmural) invasion
___ pT3: Tumor limited to the ipsilateral pleura (with or without fissure involvement) and with invasion of any of the following: Mediastinal fat; or Surface of pericardium; or Endothoracic fascia; or Solitary area of chest wall soft tissue
___ pT4: Tumor with invasion of any of the following: Chest wall bony invasion (rib); or Mediastinal organs (heart, spine, esophagus, trachea, great vessels); or Diffuse chest wall invasion; or Transmural invasion of the diaphragm or pericardium; or Direct extension to the contralateral pleura; or Presence of malignant pericardial effusion

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category
___ pN not assigned (localized pleural mesothelioma)
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No tumor involvement of regional lymph node(s)
___ pN1: Tumor involvement of ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes) regional lymph nodes
___ pN2: Tumor involvement of contralateral mediastinal, ipsilateral or contralateral supraclavicular lymph nodes

N Suffix (required only if applicable) (select all that apply)
___ Not applicable
___ (sn): Sentinel node procedure
___ (f): FNA or core needle biopsy

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s) or localized pleural mesothelioma
___ pM1: Microscopic confirmation of distant metastasis

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)
___ None identified
___ Asbestos bodies
___ Pleural plaque
___ Pulmonary interstitial fibrosis (specify pattern if discernable): _____
___ Inflammation (specify type): _____
___ Other (specify): _____

SPECIAL STUDIES (Note I)

+Immunohistochemistry (specify stains and results): _____

+Histochemistry (specify stains and results): _____

+Electron Microscopy (specify results): _____

+Other Ancillary Studies (specify types and results): _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Specimen

The International Association for the Study of Lung Cancer (IASLC) has developed an international malignant plural mesothelioma (MPM) staging database that was designed to address the limitations of the mesothelioma staging. Data analyses revealed that survival was significantly influenced by whether a curative or palliative surgical procedure was performed (median survival 18 versus 12 months, *p* <0.0001).[1] Early stage (stage I) MPM resected by extrapleural pneumonectomy (EPP) with curative intent were associated with a median survival of 40 months, whereas those managed by pleurectomy/decortication (P/D) with curative intent had a median survival of 23 months.[1] Type of surgical procedure did not impact survival in higher stage disease. It was also noted that significant variations regarding surgical nomenclature for procedures for MPM exist among thoracic surgeons.[2] The International Staging Committee of the IASLC and the International Mesothelioma Interest Group (IMIG) recommended that P/D refer to removal of all macroscopic tumor involving the parietal and visceral pleura and that the term extended P/D (or EPD) to be used to describe parietal and visceral pleurectomy together with resection of the diaphragm and /or pericardium.[2,3]

References

1. Rusch VW, Giroux D, Kennedy C et al. Initial analysis of the International Association for the Study of Lung Cancer mesothelioma database. *J Thorac Oncol*. 2012; 7:1631-1639.
2. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the International Association for the Study of Lung Cancer International Staging Committee and the International Mesothelioma Interest Group. *J Thorac Oncol*. 2011;16:1304-1312.
3. Pass H, Giroux D, Kennedy C, et al. The IASLC Mesothelioma Staging Project: improving staging of a rare disease through international participation. *J Thorac Oncol*. 2016;11(12):2082-2088.

B. Tumor Focality

The majority of malignant mesotheliomas exhibit diffuse growth and may take the form of multiple small nodules, plaque-like masses, or confluent rind-like sheets. However, a small proportion of malignant mesotheliomas are sharply circumscribed. These are designated by the term “localized malignant mesothelioma”. Localized malignant mesotheliomas appear to have a far better prognosis than their diffuse counterpart.[1] Note that current AJCC guidelines do not have a pTNM staging classification for localized pleural mesotheliomas.

References

1. Marchevsky AM, Khoor A, Walts AE, et al. Localized malignant mesothelioma, an unusual and poorly characterized neoplasm of serosal origin: best current evidence from the literature and the International Mesothelioma Panel. *Mod Pathol*. 2020 Feb;33(2):281-296.

C. Histologic Type

For consistency in reporting, the histologic classification published by the World Health Organization (WHO) is recommended.[1] Mesotheliomas are classified as epithelioid, sarcomatoid (including desmoplastic), or biphasic. Recognition and reporting of various architectural patterns, cytological features and stromal features is encouraged because of their prognostic value.[2] Desmoplastic mesothelioma is considered to

represent a variant of sarcomatoid mesothelioma. Biphasic mesotheliomas, contain both epithelioid and sarcomatoid subtypes, and each component should represent at least 10% of the tumor.[1]

The 2021 WHO classification recommends using well-differentiated papillary mesothelial tumor (WDPMT) over well-differentiated papillary mesothelioma (WDPM).[1] These are noninvasive papillary neoplasms associated with slow growth and recurrences. Survival is better than that for diffuse mesotheliomas. WDPMTs are not staged according to AJCC staging system and do not require a synoptic report.

The 2021 WHO classification introduced the concept of mesothelioma in-situ as a preinvasive single-layer surface proliferation of neoplastic mesothelial cells.[1,3] The diagnosis may be suspected in patients with recurrent effusions. The WHO considers essential diagnostic criteria to be (a) non-resolving pleural effusion, (b) no thoracoscopic or imaging evidence of tumor, and (c) a single layer of mesothelial cells (with or without atypia) on the pleural surface with loss of BAP1 and/or MTAP by immunohistochemistry and/or CDKN2A homozygous deletion by fluorescence in-situ hybridization. Multidisciplinary discussion of these cases is encouraged. Mesothelioma in-situ is not staged according to AJCC staging system and does not require a synoptic report.

References

1. WHO Classification of Tumours Editorial Board. *Thoracic tumours*. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.fr/595.
2. Nicholson AG, Sauter JL, Nowak AK, et al. EURACAN/IASLC Proposals for Updating the Histologic Classification of Pleural Mesothelioma: Towards a More Multidisciplinary Approach. *J Thorac Oncol*. 2020 Jan;15(1):29-49.
3. Churg A, Galateau-Salle F, Roden AC, et al. Malignant mesothelioma in situ: morphologic features and clinical outcome. *Mod Pathol*. 2020 Feb;33(2):297-302.

D. Histologic Grade

The 2021 WHO classification recommends grading of diffuse epithelioid mesothelioma to identify tumors that may behave aggressively.[1] A nuclear grade is assigned based on nuclear atypia and mitotic count and subsequently combined with the presence or absence of necrosis.[2,3] Low grade tumors are those exhibiting nuclear grade 1 (with or without necrosis) or nuclear grade 2 without necrosis. High grade tumors are those exhibiting nuclear grade 2 with necrosis, or nuclear grade 3 with or without necrosis. High grade tumors are those exhibiting nuclear grade 2 with necrosis, or nuclear grade 3 with or without necrosis.

Grading should be performed based on the areas showing the highest-grade features.

References

1. WHO Classification of Tumours Editorial Board. *Thoracic tumours*. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.fr/595.
2. Rosen LE, Karrison T, Ananthanarayanan V, Gallan AJ, Adusumilli PS, Alchami FS, Attanoos R, Brcic L, Butnor KJ, Galateau-Sallé F, Hiroshima K, Kadota K, Klampatsa A, Stang NL, Lindenmann J, Litzky LA, Marchevsky A, Medeiros F, Montero MA, Moore DA, Nabeshima K, Pavlisko EN, Roggli VL, Sauter JL, Sharma A, Sheaff M, Travis WD, Vigneswaran WT, Vrugt B, Walts AE, Tjota

MY, Krausz T, Husain AN. Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study. *Mod Pathol*. 2018 Apr;31(4):598-606.
3. Nicholson AG, Sauter JL, Nowak AK, et al. EURACAN/IASLC Proposals for Updating the Histologic Classification of Pleural Mesothelioma: Towards a More Multidisciplinary Approach. *J Thorac Oncol.* 2020 Jan;15(1):29-49.

E. Tumor Extent

Invasion of the endothoracic fascia is categorized as T3. The endothoracic fascia is located external to the parietal pleura beneath the muscles and ribs of the chest wall. Determining the presence or absence of endothoracic fascial invasion can be difficult on pathologic examination, because the endothoracic fascia lacks distinctive gross and histologic features. Assessment of the intactness of the endothoracic fascia is best made by the surgeon at the time of operation.

Although the American Joint Committee on Cancer (AJCC) designates a solitary focus of tumor invading the soft tissues of the chest wall as T3, it does not specifically delineate the elements that constitute the chest wall. According to the surgical literature, the constituents of the chest wall are the ribs, intercostal muscles, and associated supporting connective tissues, the latter 2 of which can be inferred to represent the chest wall soft tissues. Note that this definition does not include the layer of adipose tissue, which is sometimes referred to as extrapleural fat, that lies between the chest wall and the parietal pleura. For specimens that incorporate chest wall structures, it is recommended that the surgeon designate the location(s) of such structures to ensure optimal pathologic assessment.

Although T4 describes locally advanced, technically unresectable tumor, radical extrapleural pneumonectomy specimens may occasionally incorporate structures directly invaded by tumor that fall under the T4 designation. These should be specified under “other” and include tumor extension to the following:

- Peritoneum (through the diaphragm)
- Contralateral pleura
- Spine
- Internal surface of the pericardium
- Myocardium
- Brachial plexus

F. Treatment Effect

Induction chemotherapy or radiation before extrapleural pneumonectomy is being used in some centers for locally advanced malignant pleural mesothelioma.[1,2] Although a formal scheme for grading histologic response to neoadjuvant treatment has not been established, in applicable specimens, the percentage of residual viable tumor should be reported.

References

1. Flores RM, Krug LM, Rosenzweig KE, et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. *J Thorac Oncol*. 2006;1:289-295.

2. Cho BC, Feld R, Leighl N, et al. A feasibility study evaluating Surgery for Mesothelioma After Radiation Therapy: the 'SMART' approach for resectable malignant pleural mesothelioma. *J Thorac Oncol.* 2014 Mar;9(3):397-402.

G. Margins

Because extrapleural pneumonectomy specimens are obtained by dissection of tumor from the thorax with en bloc resection of the lung, pleura, pericardium, and diaphragm, the entire surface of the extrapleural pneumonectomy represents the surgical margin (unless otherwise specified by the operating surgeon).

H. pTNM Classification

This protocol recommends the AJCC and the International Union Against Cancer (UICC) TNM staging system shown below.[1,2] The changes introduced in the AJCC Cancer Staging Manual 8th edition and Version 9 are based on analyses of the IASLC retrospective and prospective databases.[3,4,5,6,7,8]

By AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after attempted surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (e.g., when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer. Version 9 incorporates changes in the clinical (c)T component but not the pathologic T component, to include size criteria of the tumor. No changes in the N categories were recommended by IASLC mesothelioma project in this edition.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix, and "y" and "r" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The "m" suffix indicates the presence of multiple synchronous primary tumors in a single site and is recorded in parentheses: pT(m)NM. In actuality, this is not a descriptor that readily applies to diffuse malignant pleural mesothelioma, which often exhibits a multinodular growth pattern but is best considered a single tumor for staging purposes. Because of this, the "m" descriptor is not listed as an option in this protocol case summary.

The "y" prefix indicates those cases in which classification is performed during or after initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor before multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the "r" prefix: rTNM.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (e.g., surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

References

1. AJCC Version 9 Diffuse Pleural Mesothelioma Cancer Staging System. Copyright 2024 American College of Surgeons.
2. Brierley JD, Gospodarowicz MK, Wittekind C, et al, eds. TNM Classification of Malignant Tumours. 8th ed. Oxford, UK: Wiley; 2016.
3. Pass H, Giroux D, Kennedy C, et al. The IASLC Mesothelioma Staging Project: improving staging of a rare disease through international participation. *J Thorac Oncol*. 2016;11(12):2082-2088.
4. Nowak AK, Chansky K, Rice DC, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2016;11(12):2089-2099.
5. Rice D, Chansky K, Nowak AK, et al. The IASLC Mesothelioma Staging Project: proposals for revisions of the N descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma. *J Thorac Oncol*. 2016;11(12):2100-2111.
6. Rusch VW, Chansky K, Kindler HL, et al. The IASLC Mesothelioma Staging Project: proposals for the M descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. *J Thorac Oncol*. 2016 Dec;11(12):2112-2119.
7. Gill RR, Nowak AK, Giroux DJ, et al. The International Association for the Study of Lung Cancer Mesothelioma Staging Project: Proposals for Revisions of the "T" Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol.* 2024 Mar 21:S1556-0864(24)00086-8.
8. Bille A, Ripley RT, Giroux DJ, et al. The International Association for the Study of Lung Cancer Mesothelioma Staging Project: Proposals for the "N" Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Pleural Mesothelioma. *J Thorac Oncol*. 2024 May 9:S1556-0864(24)00208-9.

I. Special Studies

Immunohistochemistry is required for a definitive diagnosis of malignant mesothelioma. The immunohistochemical approach depends on the mesothelioma morphology (epithelioid, sarcomatoid) and the type of tumors that are considered in the differential diagnosis. The 2021 WHO classification continues to recommend the combined use of a minimum of two mesothelial markers and two carcinoma markers.[1] Based on the specificity and sensitivity, the best positive mesothelial markers include calretinin, cytokeratins 5/6, WT-1, and D2-40. BerEP4 or MOC31, B72.3, CEA, and BG8 are the most frequently used to diagnose carcinoma.[1] No specific panel is recommended, and the International Mesothelioma Panel recommends that each laboratory should choose antibodies with a sensitivity and specificity of at least 80%.[2] The College of American Pathologists does not endorse a specific panel of markers for the evaluation of malignant mesothelioma. If sarcoma is considered in the differential diagnosis, appropriate immunohistochemical, cytogenetic and molecular workup should be performed. Diagnostic role of histochemistry and electron microscopy is very limited because immunohistochemistry is widely available and frequently sufficient to establish the diagnosis of malignant mesothelioma.

References

1. WHO Classification of Tumours Editorial Board. *Thoracic tumours*. Lyon (France): International Agency for Research on Cancer; 2021. (WHO classification of tumours series, 5th ed.; vol. 5). https://publications.iarc.fr/595.
2. Husain AN, Colby TV, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2017 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med*. 2018 Jan; 142(1):89-108.