National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Malignant Pleural Mesothelioma

NCCN Evidence Blocks™

Version 1.2020 — November 27, 2019

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NCCN Evidence Blocks™

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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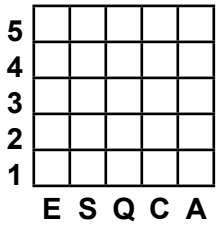
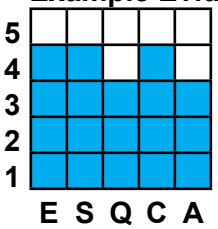
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

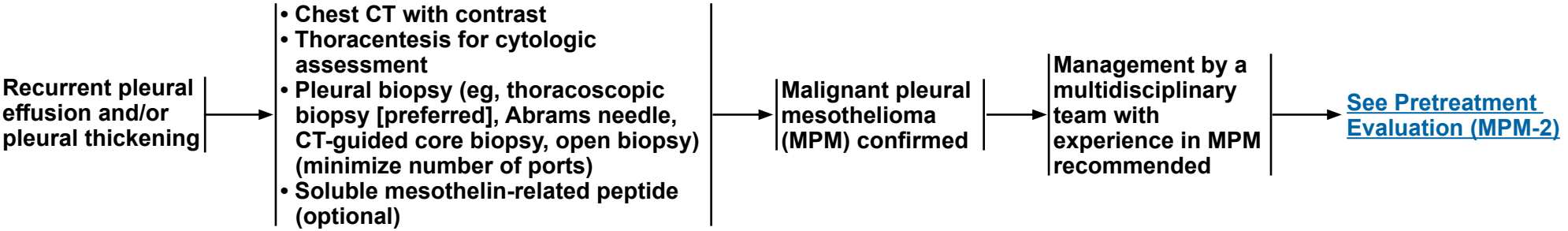
Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

INITIAL EVALUATION[a]



[a] There are no data to suggest that screening improves survival.

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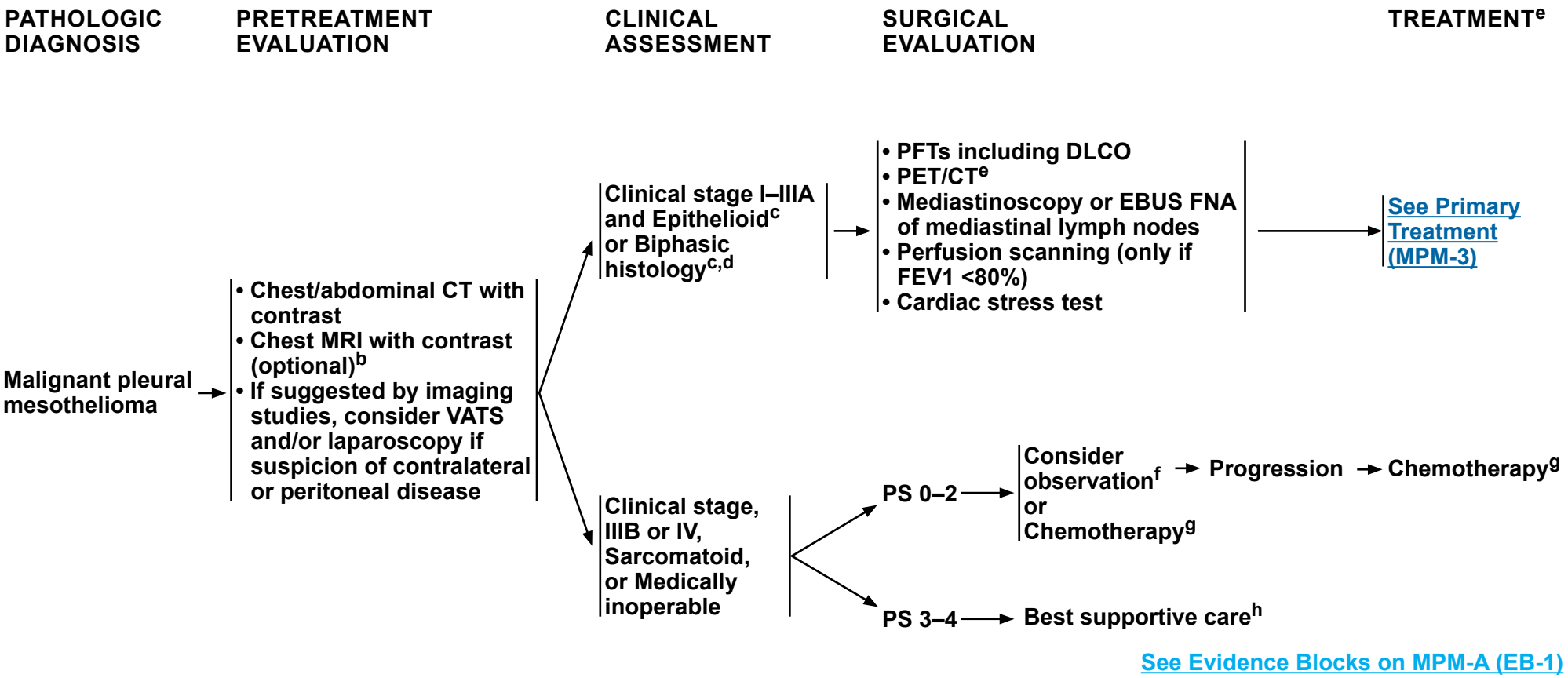

See Evidence Blocks on MPM-A (EB-1)

[b] For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[c] Surgery should be considered for biphasic histology if the patient has early-stage disease.
[d] If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.
[e] If PET/CT is to be done, recommend obtaining PET/CT before pleurodesis. Confirm diagnosis of MPM prior to pleurodesis. If MPM is suspected, consider evaluation by a multidisciplinary team with expertise in MPM.
[f] Observation may be considered for patients who are asymptomatic with minimal burden of disease if chemotherapy is planned at the time of symptomatic or radiographic progression.
[g] See Principles of Systemic Therapy (MPM-A).
[h] See Principles of Supportive Care (MPM-B).

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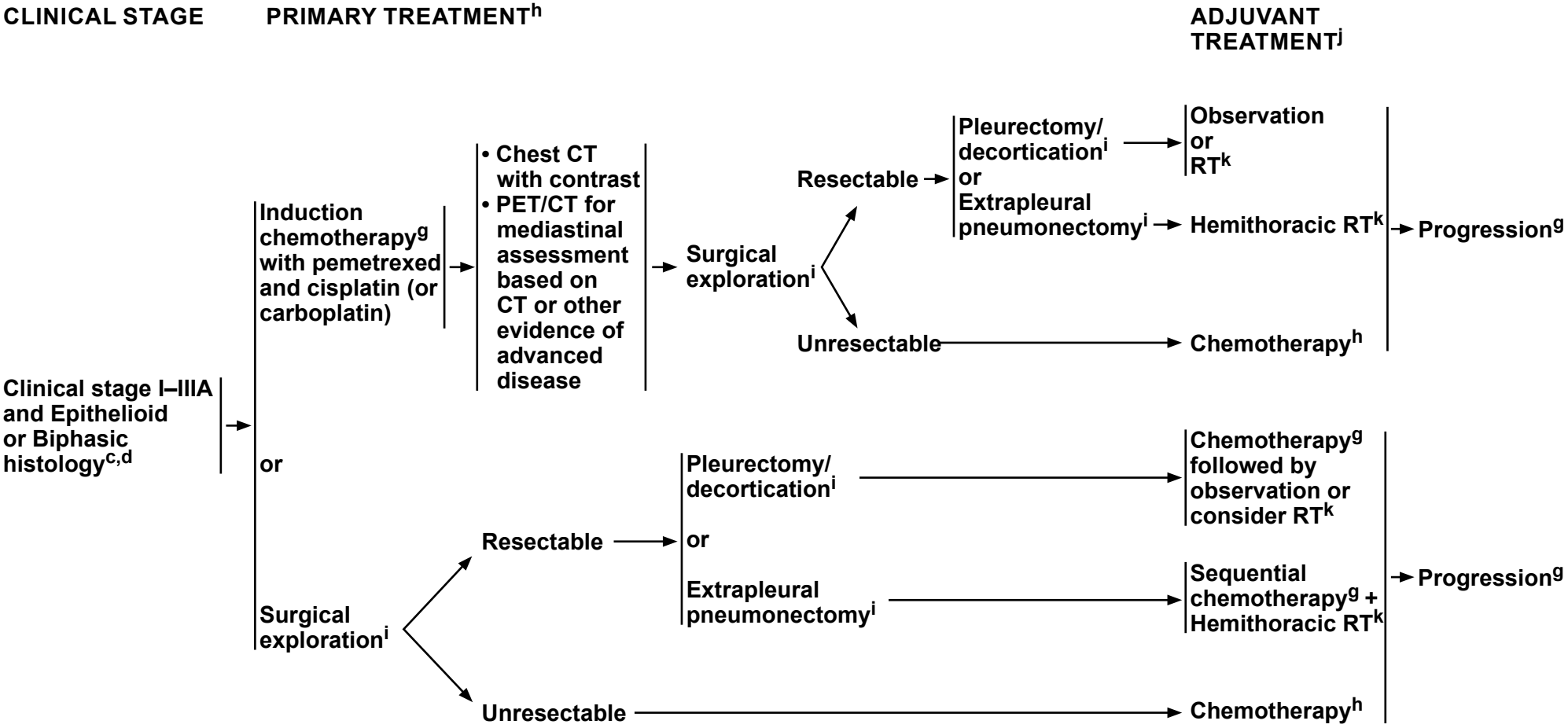

See Evidence Blocks on MPM-A (EB-1)

[c] Surgery should be considered for biphasic histology if the patient has early-stage disease.
[d] If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.
[g] See Principles of Systemic Therapy (MPM-A).
[h] See Principles of Supportive Care (MPM-B).
[i] See Principles of Surgery (MPM-C).
[j] See NCCN Guidelines for Survivorship.
[k] See Principles of Radiation Therapy (MPM-D).

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PRINCIPLES OF SYSTEMIC THERAPY

FIRST-LINE CHEMOTHERAPY REGIMENS

Preferred

- **Pemetrexed[a] 500 mg/m² day 1**
  Cisplatin 75 mg/m² day 1
  Administered every 3 weeks (category 1)[1]
- **Pemetrexed[a] 500 mg/m² day 1**
  Cisplatin 75 mg/m² day 1
  Bevacizumab[b] 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression (category 1)[2,c]

Other Recommended

- **Pemetrexed[a] 500 mg/m² day 1**
  Carboplatin AUC 5 day 1[3-5,d]
  ± bevacizumab[b] 15 mg/kg day 1[6]
  Administered every 3 weeks for 6 cycles
  ± maintenance bevacizumab 15 mg/kg (if bevacizumab given in combination with pemetrexed and carboplatin) every 3 weeks until disease progression[c]

Useful in Certain Circumstances

- **Gemcitabine 1000–1250 mg/m² days 1, 8, and 15**
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[7,8]
- **Pemetrexed[a] 500 mg/m² every 3 weeks[9]**
- **Vinorelbine 25–30 mg/m² weekly[10]**

SUBSEQUENT SYSTEMIC THERAPY

Preferred

- **Pemetrexed[a] (if not administered as first-line) (category 1)[11]**
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[12]
- **Nivolumab ± ipilimumab[13,14]**
- **Pembrolizumab[15,16]**

Other Recommended

- **Vinorelbine[17,18]**
- **Gemcitabine[18-20]**

See Evidence Blocks on MPM-A (EB-1)

References on MPM-A (2 of 2)

[a] Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[21]
[b] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[c] The combination regimen of pemetrexed/cisplatin/bevacizumab or pemetrexed/carboplatin/bevacizumab is only for unresectable disease.
[d] Appropriate for patients not eligible for cisplatin.

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EVIDENCE BLOCKS FOR SYSTEMIC THERAPY

First-Line Combination Chemotherapy

	Clinical stage IV, sarcomatoid, or medically inoperable MPM PS 0-2 (MPM-2)	Induction chemotherapy for medically operable clinical stage I-III (MPM-3)	Unresectable clinical stage I-III (MPM-3)	Postoperative chemotherapy for clinical stage I-III not receiving induction therapy (MPM-3)
Carboplatin + pemetrexed				
Carboplatin + pemetrexed + bevacizumab followed by maintenance bevacizumab		—		—
Cisplatin + gemcitabine		—		
Cisplatin + pemetrexed				
Cisplatin + pemetrexed + bevacizumab followed by maintenance bevacizumab		—		—
Pemetrexed		—		
Vinorelbine		—		

Subsequent Systemic Therapy

Pemetrexed	
Vinorelbine	
Gemcitabine	
Nivolumab + ipilimumab	
Nivolumab	
Pembrolizumab	

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PRINCIPLES OF SYSTEMIC THERAPY
REFERENCES

[1] Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636-2644.
[2] Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, Phase 3 trial. Lancet 2016;387:1405-1414.
[3] Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma. Ann Oncol 2008;19:370-373.
[4] Ceresoli GL, Zucali PA, Favaretto AG, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. J Clin Oncol 2006;24:1443-1448.
[5] Santoro A, O'Brien ME, Stahel RA, et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemonaive patients with malignant pleural mesothelioma. J Thorac Oncol 2008;3:756-763.
[6] Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab as first-line therapy in malignant pleural mesothelioma. Br J Cancer 2013;109:552-558.
[7] Nowak AK, Byrne MJ, Willianson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 2002;87:491-496.
[8] Van Haarst JM, Baas J, Manegold CH, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. Br J Cancer 2002;86:342-345.
[9] Taylor P, Castagneto B, Dark G, et al. Single-agent pemetrexed for chemonaive and pretreated patients with malignant pleural mesothelioma: results of an International Expanded Access Program. J Thorac Oncol 2008;3:764-771.
[10] Muers MF, Stephens RJ, Fisher P, et al. Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial. Lancet 2008;371:1685-1694.
[11] Jassem J, Ramlau R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. J Clin Oncol 2008;26:1698-1704.
[12] Zucal PA, Simonelli M, Michetti G, et al. Second-line chemotherapy in malignant pleural mesothelioma: results of a retrospective multicenter survey. Lung Cancer 2012;75:360-367.
[13] Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomized, non-comparative, phase 2 trial. Lancet Oncol 2019;20:239-253.
[14] Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, single-arm, phase 2 trial. Lancet Respir Med 2019;7:260-270.
[15] Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. Lancet Oncol 2017;18:623-630.
[16] Metaxas Y, Rivalland G, Mauti LA, et al. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. J Thorac Oncol 2018;13:1784-1791.
[17] Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. Lung Cancer 2009;63:94-97.
[18] Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. Lung Cancer 2014;84:271-274.
[19] Manegold C, Symanowski J, Gatzemeier U, et al. Second-line (post-study) chemotherapy received by patients treated in the phase III trial of pemetrexed plus cisplatin versus cisplatin alone in malignant pleural mesothelioma. Ann Oncol 2005;16:923-927.
[20] van Meerbeeck JP, Baas P, Debruyne C, et al. A phase II study of gemcitabine in patients with malignant pleural mesothelioma. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Cancer 1999;85:2577-2582.
[21] Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer 2009;64:211-218.

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PRINCIPLES OF SUPPORTIVE CARE

- **Pleural effusions: Talc pleurodesis or pleural catheter, if required for management of pleural effusion.[1] Drainage is preferred for candidates with potentially operable disease; drainage or pleurodesis are both options for patients with inoperable disease.**
- **Smoking cessation counseling and intervention (http://www.smokefree.gov/). See the NCCN Guidelines for Lung Cancer Screening.**
- **Pain management: See NCCN Guidelines for Adult Cancer Pain**
- **Nausea/vomiting: See NCCN Guidelines for Antiemesis**
- **Psychosocial distress: See NCCN Guidelines for Distress Management**
- **See NCCN Guidelines for Palliative Care as indicated**

[1] If PET/CT is to be done, recommend obtaining PET/CT before pleurodesis. Confirm diagnosis of MPM prior to pleurodesis. If MPM is suspected, consider evaluation by a multidisciplinary team with expertise in MPM.

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PRINCIPLES OF SURGERY[1]

- **Surgical resection should be performed on carefully evaluated patients by thoracic surgeons with experience in managing MPM.**
- **Decisions regarding surgical options for treatment are highly dependent on accurate histology. Pleural biopsy for diagnosis should provide enough tissue for differentiation of epithelioid, sarcomatoid, or mixed histology and clearly exclude metastatic pleural involvement of another primary. Cytology is generally not considered adequate for important histologic differentiation required for treatment decisions**
- **For patients being considered for surgery, a single-port thoracoscopy on the line of the potential incision is recommended.**
- **The goal of surgery is complete gross cytoreduction of the tumor. The goal of cytoreductive surgery is "macroscopic complete resection." In other words, removal of ALL visible or palpable tumors. In cases where this is not possible, such as in multiple sites of chest wall invasion, surgery should be aborted. If it is possible to remove most of the gross disease to help with postoperative management, with a minimal impact on morbidity, then surgery should be continued.**
- **The surgical choices are: 1) pleurectomy/decortication (P/D) with mediastinal lymph node sampling, which is defined as complete removal of the pleura and all gross tumor ± en-bloc resection of pericardium and/or diaphragm with reconstruction; and 2) extrapleural pneumonectomy (EPP), which is defined as en-bloc resection of the pleura, lung, ipsilateral diaphragm, and often pericardium. Mediastinal node sampling should be performed with a goal to obtain at least 3 nodal stations.**
- **For early-stage disease (confined to the pleural envelope, no N2 lymph node involvement) with favorable histology (epithelioid), P/D may be safer than EPP but it is unclear which operation is oncologically better. There is controversy regarding choice of procedure that needs to be weighed, taking into account tumor histology, distribution, the patient's pulmonary reserve, and availability of adjuvant and intraoperative strategies. P/D and EPP are each reasonable surgical treatment options and should be considered in select patients for complete gross cytoreduction.[2-5]**
- **If N2 disease is identified, prognosis with surgery (and other therapy) is substantially diminished. Surgical resection should only be considered in the setting of a clinical trial or at a center with expertise in MPM.**
- **If technically appropriate for even more advanced disease, lung-sparing operations like P/D reduce the risk for perioperative mortality and may be acceptable in terms of achieving complete macroscopic resection. P/D can provide excellent symptomatic control of recurrent pleural effusions.**
- **Intraoperative adjuvant therapy is still under investigation but may be considered as part of a reasonable multidisciplinary approach to this locally aggressive disease.**
- **After recovery from surgery, patients should be referred for adjuvant therapy, which may include chemotherapy and RT depending on whether any preoperative therapy was used and on the pathologic analysis of the surgical specimen.**

[1] 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;6:1304-1312.
[2] Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 663 patients. J Thorac Cardiovasc Surg 2008;135:620-626.
[3] Spaggiari L, Marulli G, Boyolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. Ann Thorac Surg 2014;97:1859-1865.
[4] Flores RM, Riedel E, Donington JS, et al. Frequency of use and predictors of cancer-directed surgery in the management of malignant pleural mesothelioma in a community-based (Surveillance, Epidemiology, and End Results [SEER]) population. J Thorac Oncol 2010;5:1649-1654.
[5] Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763-772.

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PRINCIPLES OF RADIATION THERAPY

General Principles

- Recommendations regarding RT should be made by radiation oncologists with experience in managing MPM.
- The best timing for delivering RT after surgical intervention and/or in conjunction with chemotherapy should be discussed in a multidisciplinary team including radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists.
- For patients with resectable MPM who undergo EPP, adjuvant RT can be recommended for patients with good performance status (PS) to improve local control.[1-6]
- PET scanning for treatment planning can be used as indicated.
- Prophylactic RT is not routinely recommended to prevent instrument-tract recurrence after pleural intervention.[7]
- RT is an effective palliative treatment for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with mesothelioma.
- When there is limited or no resection of disease, delivery of high-dose RT to the entire hemithorax in the setting of an intact lung has not been shown to be associated with significant survival benefit, and the toxicity is significant.[1,5,6] RT under such circumstances after P/D is usually not recommended. Hemithoracic intensity-modulated RT (IMRT) after P/D may be considered in centers with experience and expertise in these methods.[8]
- Acronyms and abbreviations related to RT are the same as listed in the Principles of Radiation Therapy for NCCN Guidelines for Non-Small Cell Lung Cancer.
- Advanced technologies may be used, such as image-guided RT (IGRT) for treatment involving IMRT/stereotactic radiosurgery (SRS)/ stereotactic body RT (SBRT).

Radiation Dose and Volume

- The dose of radiation should be based on the purpose of the treatment.
  See Recommended Doses for Radiation Therapy (MPM-D 2 of 3).
- The dose of radiation for adjuvant therapy following EPP should be 45–60 Gy in 1.8–2.0 Gy based on the margin status. A dose of 54 Gy given to the entire hemithorax, the thoracotomy incision, and sites of chest drains was well-tolerated.[6,9] When it is challenging to deliver 45 Gy, every effort should be made to deliver a minimum dose of 40 Gy.[1]
- A dose ≥60 Gy should be delivered to macroscopic residual tumors if the doses to adjacent normal structures are limited to their tolerances. In addition to covering the surgical bed within the thorax, the volume of postoperative radiation should also include the surgical scars and biopsy tracks in the chest wall.[10-12]
- Daily doses of 4 Gy appear to be more efficacious than fractions of less than 4 Gy in providing relief from chest pain associated with mesothelioma,[11,13] although the optimal daily and total dose of RT for palliative purposes remains unclear.
- For patients with residual tumors, some experienced investigators have used brachytherapy or intraoperative external beam RT (EBRT) in combination with surgery.

See Radiation Techniques (MPM-D 2 of 3)
See References (MPM-D 3 of 3)

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PRINCIPLES OF RADIATION THERAPY

Recommended Doses for Radiation Therapy

Treatment type	Total dose	Fraction size	Treatment duration
Postoperative after EPP Higher dose to higher risk areas	45–60 Gy	1.8–2 Gy	5–6 weeks
Palliative			
Chest wall pain from recurrent nodules	20–40 Gy or 30 Gy	≥4 Gy 3 Gy	1–2 weeks 2 weeks
Multiple brain or bone metastases	30 Gy	3 Gy	2 weeks
Post pleurectomy/decortication Higher dose to higher risk areas	45–60 Gy	1.8–2 Gy	5–6 weeks

After EPP, RT should only be considered for patients who meet the following criteria: ECOG PS ≤1; good functional pulmonary status; good function of contralateral kidney confirmed by renal scan; and absence of disease in abdomen, contralateral chest, or elsewhere. Patients who are on supplemental oxygen should not be treated with adjuvant RT.

Radiation Techniques

- Use of conformal radiation technology (IMRT) is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance.[8,14]
- CT simulation-guided planning using either IMRT or conventional photon/electron RT is acceptable.[8] IMRT is a promising treatment technique that allows for a more conformal high-dose RT and improved coverage to the hemithorax. IMRT or other modern technology (such as tomotherapy or protons) should only be used in experienced centers or on protocol. When IMRT is applied, the NCI and ASTRO/ACR IMRT guidelines should be strictly followed.[15,16] Special attention should be paid to minimize radiation to the contralateral lung,[17] as the risk of fatal pneumonitis with IMRT is excessively high when strict limits are not applied.[18] The mean lung dose should be kept as low as possible, preferably <8.5 Gy. The low-dose volume should be minimized.[19]
- The gross tumor volume (GTV) should include any grossly visible tumor. Surgical clips (indicative of gross residual tumor) should be included for postoperative adjuvant RT.
- The clinical target volume (CTV) for adjuvant RT after EPP or P/D should encompass the entire pleural surface (for partial resection cases), surgical clips, and any potential sites with residual disease.
- Extensive elective nodal irradiation (ENI) (entire mediastinum and bilateral supraclavicular nodal regions) is not recommended.
- The planning target volume (PTV) should consider the target motion and daily setup errors. The PTV margin should be based on the individual patient's motion, simulation techniques used (with and without inclusion motion), and reproducibility of each clinic's daily setup.

See General Principles and Radiation Dose and Volume (MPM-D 1 of 3)
See References (MPM-D 3 of 3)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Table 1. **Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to the ipsilateral parietal pleura with or without involvement of: -visceral pleura -mediastinal pleura -diaphragmatic pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: -Involvement of diaphragmatic muscle -Extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but **potentially resectable** tumor. Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura), with at least one of the following features: -Involvement of the endothoracic fascia -Extension into the mediastinal fat -Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall -Nontransmural involvement of the pericardium
T4	Locally advanced **technically unresectable** tumor. Tumor involving all ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: -Diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction -Direct transdiaphragmatic extension of the tumor to the peritoneum -Direct extension of tumor to the contralateral pleura -Direct extension of tumor to mediastinal organs -Direct extension of tumor into the spine -Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal) lymph nodes
N2	Metastases in the contralateral mediastinal, ipsilateral, or contralateral supraclavicular lymph nodes

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis present

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage IA	T1	N0	M0
Stage IB	T2-T3	N0	M0
Stage II	T1-T2	N1	M0
Stage IIIA	T3	N1	M0
Stage IIIB	T1-T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/01/19

Table of Contents

Overview

Mesothelioma is a rare cancer originating in mesothelial surfaces of the pleura and other sites that is estimated to occur in approximately 2,500 people in the United States every year.[1-4] These NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) focus on malignant pleural mesothelioma (MPM), which is the most common type (81%). Mesothelioma can also occur in the lining of other sites, such as the peritoneum (8%), pericardium, and tunica vaginalis testis.[5-7] MPM is difficult to treat, because most patients have advanced disease at presentation. Median overall survival is approximately 1 year in patients with MPM, and 5-year overall survival is about 10%; cure is rare.[2,8-11] MPM occurs mainly in older men (median age at diagnosis, 72 years) who have been exposed to asbestos, although it occurs decades after exposure (20–40 years later).[12-14]

These NCCN Guidelines® for Malignant Pleural Mesothelioma were first published in 2010 and have been subsequently updated every year. The *Summary of the Guidelines Updates* section in the algorithm briefly describes the new changes for 2019, which are described in greater detail in this revised Discussion text; recent references have been added. Additional supplementary material in the NCCN Guidelines for Malignant Pleural Mesothelioma includes the *Principles of Systemic Therapy*, *Principles of Supportive Care, Principles of Surgery*, and *Principles of Radiation Therapy.* These NCCN Guidelines for Malignant Pleural Mesothelioma were developed and are updated by panel members who are also on the panel for the NCCN Guidelines for Non-Small Cell Lung Cancer.

The incidence of MPM is decreasing in men in the United States, because asbestos use has decreased since the 1970s; however, the United States still has more reported cases and deaths than anywhere else in the world.[1,15-17] The mortality burden from asbestos-related diseases in the United States did not change from 1999 to 2015.[8,18] Although asbestos is no longer mined in the United States, it is still imported.[17] The incidence of MPM is increasing in other countries such as Russia, Western Europe, China, and India.[3,16,19-24] Mortality rates from MPM are highest in the United Kingdom, Netherlands, and Australia; mortality rates are increasing in Poland, Spain, China, Japan, Argentina, Republic of Korea, and Brazil.[10,19,20,25] Russia, China, Brazil, and Canada are the top producers of asbestos.[26]

Although most mesothelioma is linked to asbestos exposure, reports suggest that ionizing radiation may also cause mesothelioma, such as in patients previously treated with mantle radiation for Hodgkin lymphoma.[27-37] Two meta-analyses suggest that non-occupational exposure to asbestos is a risk factor for MPM.[38,39] Data also suggest that erionite (a mineral that may be found in gravel roads) is associated with mesothelioma.[40-43] Genetic factors may also play a role in MPM, with rare families carrying a germline mutation in the *BRCA1*-associated protein-1 (*BAP1*) gene.[40,44-50] Smoking is not a risk factor for mesothelioma.[51] However, patients who smoke and have been exposed to asbestos are at increased risk for lung cancer.[52] Patients who smoke should be encouraged to quit because smoking impedes treatment (eg, delays wound healing after surgery) (see the NCCN Guidelines® for Smoking Cessation, available at www.NCCN.org).[53]

The histologic subtypes of mesothelioma include epithelioid (most common), sarcomatoid, and biphasic (mixed) epithelioid and sarcomatoid.[4,54,55] Patients with epithelioid histology have better outcomes than those with either mixed or sarcomatoid histologies. Some patients who have been exposed to asbestos only have benign pleural disease, although they may have significant chest pain.[56,57] Although screening for mesothelioma has been studied in patients at high risk (ie, those with asbestos exposure), these NCCN Guidelines do

not recommend screening for MPM because it has not been shown to decrease mortality (see *Initial Evaluation* in the algorithm).[26,52,58-64] Note that data and guidelines about screening for lung cancer with low-dose CT do not apply to MPM; there are no data to suggest that screening with low-dose CT improves survival for patients with MPM.[26,52,65,66]

Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature on mesothelioma using the following search term: malignant pleural mesothelioma. The PubMed database was chosen, because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, then recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage (available at www.NCCN.org).

Diagnosis

Patients with suspected MPM often have dyspnea and chest pain; they may also have pleural effusion, fatigue, insomnia, cough, chest wall mass, loss of appetite, and weight loss (see the NCCN Guidelines for Adult Cancer Pain, available at www.NCCN.org).[25,67,68] Patients with MPM often have a high symptom burden when compared with patients who have other types of cancer. Patients often present without distant metastases because symptoms such as chest pain and/or dyspnea are associated with local disease; CNS metastases are uncommon.[58] In patients with recurrent pleural effusion and/or pleural thickening, the recommended initial evaluation for suspected MPM includes: 1) CT of the chest with contrast; 2) thoracentesis for cytologic assessment of the effusion; and 3) pleural biopsy (eg, thoracoscopic biopsy [preferred]) (see *Initial Evaluation* in the algorithm).[25,26,58,69-73] However, cytologic samples are often negative even when patients have MPM.[74,75] Fine-needle aspiration (FNA) is not recommended for diagnosis.[25] Talc pleurodesis or pleural catheter may be needed for management of pleural effusion.[58,76-85] Drainage is preferred for patients with potentially operable disease, whereas either drainage or pleurodesis are options for patients who are medically inoperable.[76] Soluble mesothelin-related peptide (SMRP) levels may also be assessed, and these levels may correlate with disease status;[86-89] osteopontin does not appear to be as useful for diagnosis.[58,90-94] Other potential diagnostic biomarkers are being assessed.[59-61,95-99]

It can be difficult to distinguish malignant from benign pleural disease and also to distinguish MPM from other malignancies such as metastatic adenocarcinoma, sarcoma, or other metastases to the pleura.[21,100-107] On CT, thymoma metastatic to the pleura can mimic MPM; however, pleural effusion does not typically occur with thymoma. Cytologic samples of pleural fluid are often negative or inconclusive, but diagnosis can sometimes be made using cytology.[58,74,75,108,109] Calretinin, WT-1, D2-40, and cytokeratin (CK) 5/6 are useful immunohistochemical markers for the diagnosis of MPM, as are markers that typically are positive in pulmonary adenocarcinoma and negative in mesothelioma (eg, thyroid transcription factor 1 [TTF-1],

carcinoembryonic antigen [CEA]) (see *Protocol for the Examination of Specimens From Patients With Malignant Pleural Mesothelioma* from the College of American Pathologists [CAP]).[58,74,101,104,106,110-112]

Management

The NCCN Guidelines recommend that patients with MPM be managed by a multidisciplinary team with experience in MPM. Treatment options for patients with MPM include surgery, radiation therapy (RT), and/or chemotherapy.[4] Select patients with medically operable disease are candidates for multimodality therapy, including those with clinical stages I to IIIA and good performance status (PS).[113-119] Definitive RT alone is not recommended for unresectable MPM; chemotherapy alone is recommended in this setting for patients with PS 0 to 2 (see *Treatment* in the algorithm).[120,121] Appropriate patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic imaging specialists, and pulmonologists to assess if they are candidates for multimodality treatment.

Pretreatment evaluation for patients diagnosed with MPM is performed to stage patients and to assess whether patients are candidates for surgery. This evaluation includes: 1) chest and abdominal CT with contrast; and 2) FDG-PET/CT but only for patients being considered for surgery.[69,70,122] Video-assisted thoracoscopic surgery (VATS) or laparoscopy can be considered if contralateral or peritoneal disease is suspected.[123] PET/CT scans should be obtained before pleurodesis if practical, because talc produces pleural inflammation, which can affect the FDG avidity (ie, false-positive result).[124-126] However, PET/CT scans are mainly used to assess for metastatic disease. If surgical resection is being considered, mediastinoscopy or endobronchial ultrasonography (EBUS) FNA of the mediastinal lymph nodes is recommended.[127,128] The following tests may be performed if suggested by imaging: 1) laparoscopy to rule out transdiaphragmatic extension (eg, extension to the peritoneum is indicative of stage IV [unresectable] disease); and 2) chest MRI with contrast to evaluate possible chest wall, spinal, diaphragmatic, or vascular involvement.

Surgical staging is performed using the International Mesothelioma Interest Group (IMIG) TNM staging system (see *Staging* in the algorithm), which was approved by the AJCC.[129-131] The AJCC cancer staging system (8th edition) became effective on January 1, 2018.[132] Some of the changes in the AJCC staging (8th edition) for MPM include: 1) T3 and T4 are now classified as stage IIIB, regardless of N status; 2) former N3 nodes are now classified as N2; 3) former N2 nodes are now classified as N1; and 4) T1a and T1b are now classified as T1.[58,132,133] Clinical staging only is done for patients who are not candidates for surgery. It is difficult to clinically stage patients using CT or MRI; therefore, patients who have surgery may be upstaged.

Most patients have advanced disease at presentation. However, it is difficult to accurately stage patients before surgery. Understaging is common with PET/CT.[126,134] However, PET/CT is useful for determining whether metastatic disease is present.[134,135] Consideration of surgical resection is recommended for patients with clinical stage I to IIIA MPM who are medically operable and can tolerate the surgery. Patients with clinical stage I to IIIA MPM can be evaluated for surgery using pulmonary function tests (PFTs), including diffusing capacity for carbon dioxide (DLCO), perfusion scanning (if forced expiratory volume in 1 second [FEV1] <80%), and cardiac stress tests (see *Surgical Evaluation* in the algorithm). Multimodality therapy (ie, chemotherapy, surgery, RT) is recommended for medically operable patients with clinical stages I to IIIA MPM (see *Treatment* in the algorithm).

Chemotherapy alone is recommended for patients with PS 0 to 2 who are not operable or refuse surgery and those with clinical stage IIIB to IV MPM, regardless of histology; best supportive care is recommended

for patients with PS 3 to 4 (see *Chemotherapy* in this Discussion and *Principles of Systemic Therapy* and *Principles of Supportive Care* in the algorithm). Observation for progression may be considered for patients with PS 0 to 2 who are asymptomatic with minimal burden of disease if chemotherapy is planned when progression occurs (either radiologic or symptomatic progression). Pleural effusion can be managed using thoracoscopic talc pleurodesis or placement of a drainage catheter.[58,76-81,85,136-138] Therapeutic/palliative thoracentesis can also be used to remove pleural fluid and thus decrease dyspnea either before treatment or for patients who are not candidates for more aggressive treatment.[25]

Surgery

Surgery is recommended for certain patients with stage I to IIIA MPM who are medically operable.[139] For the 2019 update (Version 1), the NCCN Panel now recommends that surgery should be considered for patients with clinical stage I to IIIA MPM; however, surgery is generally not an option for those with stage IIIB or IV MPM regardless of histology.[140] It is essential that patients receive a careful assessment before surgery is performed.

Surgical resection for patients with MPM can include either 1) pleurectomy/decortication (P/D; also known as total pleurectomy, lung-sparing surgery), which is complete removal of the involved pleura and all gross tumor; or 2) extrapleural pneumonectomy (EPP), which is en-bloc resection of the involved pleura, lung, ipsilateral diaphragm, and often the pericardium (see *Principles of Surgery* in the algorithm).[141] Extended P/D refers to the resection of the diaphragm and pericardium in addition to total pleurectomy.[141] Mediastinal nodal dissection is recommended in patients having either P/D or EPP; at least 3 nodal stations should be obtained (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). The surgical goal for MPM is cytoreductive surgery to achieve macroscopic complete resection by removing all visible or palpable tumors.[142,143] If macroscopic complete resection is not possible—such as patients with multiple sites of chest wall invasion—then surgery should be aborted. However, surgery should be continued—if most of the gross disease can be removed—to help with postoperative management and if there will be a minimal impact on morbidity.

The choice of surgery for MPM is controversial, because data from randomized controlled trials are not available.[4,25,58,139,144-152] Neither EPP nor P/D will yield an R0 resection.[4,153,154] EPP would often be required to remove all gross tumor in patients with stages II to IIIA MPM.[68] However, EPP is associated with higher morbidity and mortality.[148,155] P/D (ie, lung-preserving surgery) is safer than EPP.[155-162] A retrospective analysis (n = 663) suggested that survival was greater after P/D than after EPP, but this analysis may have been confounded by patient selection.[4,160] A large meta-analysis (n = 2903) suggests that 30-day mortality is improved with P/D versus EPP; 2-year mortality was similar between the arms.[12,148] Another meta-analysis (n = 500) suggests that P/D is associated with decreased 30-day mortality and complications (especially supraventricular arrhythmia) when compared with EPP.[145] Lung-sparing options, such as P/D, reduce the risk for perioperative mortality when compared with EPP and yield either equal or better long-term survival than non-surgical therapy in patients with more advanced disease.[153,163]

A feasibility trial (Mesothelioma and Radical Surgery [MARS]) assessed whether patients treated with induction chemotherapy would accept randomization to EPP or no surgery; 112 patients were enrolled in the trial, and 50 patients were randomized.[164] The authors concluded that due to the observed high rate of surgical mortality, EPP was not beneficial when compared with chemotherapy treatment alone.

However, these results were controversial because survival was not the primary outcome of the study, the sample size was small, and the surgical mortality was higher than expected.[165] An Australian retrospective study (540 patients) reported that several factors yielded increased survival for select patients, including EPP, surgeon experience, and treatment with pemetrexed.[166]

The NCCN Panel feels that P/D and EPP are reasonable surgical options that should be considered in select patients to achieve complete gross cytoreduction.[148,160,164,167,168] Although P/D may be safer than EPP, it is not clear which operation is oncologically better. When surgery is indicated, the choice between P/D and EPP should be made based on several factors including tumor histology and distribution, stage, pulmonary reserve, surgical experience and expertise, and availability of adjuvant and intraoperative strategies.[9,168] In patients who are medically operable, the decision about whether to do a P/D or an EPP may not be made until surgical exploration. P/D may be more appropriate for patients with advanced MPM who cannot tolerate an EPP.[156] P/D may also be useful for symptom control (eg, patients with entrapped lung syndrome, recurrent pleural effusions).[26] The NCCN Panel does not generally recommend surgery for patients with stage IIIB to IV MPM regardless of histology; chemotherapy is recommended for these patients (see *Chemotherapy* in this Discussion and *Treatment* in the algorithm). In addition, surgery is generally not recommended for patients with N2 disease unless performed at a center of expertise or in a clinical trial.

Chemotherapy

Chemotherapy is recommended as part of a multimodality regimen for patients with medically operable MPM (see *Treatment* and *Principles of Systemic Therapy* in the algorithm). Patients with medically operable stage I to IIIA MPM can receive chemotherapy either before or after surgery. Chemotherapy alone is recommended for patients with stage IIIB or IV MPM (PS 0–2), medically inoperable stages I to IV MPM, or those who refuse surgery.[149,169-171] Pemetrexed-based chemotherapy can also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[5,172] Trimodality therapy—using chemotherapy, surgery, and hemithoracic RT—has been used in patients with MPM.[115-118,173-176] Median survival of up to 20 to 29 months has been reported for patients who complete trimodality therapy.[116,176] Nodal status and response to chemotherapy can affect survival.[116,119] In patients who do not receive induction chemotherapy before EPP, postoperative sequential chemotherapy with hemithoracic RT is recommended. Intraoperative adjuvant therapies—such as hyperthermic pleural lavage, photodynamic therapy, or heated chemotherapy—have also been studied.[177-186]

First-Line Therapy

A combined first-line regimen using cisplatin/pemetrexed is currently the only regimen approved by the FDA.[187-190] A phase 3 randomized trial assessed cisplatin/pemetrexed versus cisplatin alone in patients who were not candidates for surgery; the combined regimen increased survival by 2.8 months when compared with cisplatin alone (12.1 vs. 9.3 months, *P*=.02).[189] Based on this trial and the FDA approval, the NCCN Panel recommends cisplatin/pemetrexed (category 1) for patients with MPM. A multicenter phase 3 randomized trial (IFCT-GFPC-0701 MAPS) compared adding bevacizumab to cisplatin/pemetrexed (with maintenance bevacizumab) versus cisplatin/pemetrexed alone for patients with unresectable MPM and PS 0 to 2 who did not have bleeding or thrombosis.[191] Overall survival was increased in the bevacizumab plus chemotherapy arm by 2.7 months when compared with chemotherapy alone (18.8 vs. 16.1 months; HR = 0.77; *P* = .0167). Grade 3 to 4 adverse events were reported in 71% (158/222) of patients receiving the bevacizumab regimen when compared with 62%

(139/224) of those receiving cisplatin/pemetrexed alone. More grade 3 or higher hypertension (23% vs. 0%), grade 3 proteinuria (3.1% vs. 0%), and grade 3 to 4 thrombotic events (6% vs. 1%) were observed in patients receiving the triplet arm. The NCCN Panel recommends (category 1) bevacizumab, cisplatin, and pemetrexed followed by maintenance bevacizumab for bevacizumab-eligible patients with unresectable MPM based on this trial (see *Principles of Systemic Therapy* in the algorithm).[191] Contraindications to bevacizumab include uncontrolled hypertension, risk for bleeding or clotting, and substantial cardiovascular morbidity.[58]

Other acceptable first-line combination chemotherapy options recommended by NCCN include: 1) pemetrexed/carboplatin, which was assessed in 3 large phase 2 studies (median survival = 12.7, 14, and 14 months, respectively);[192-194] or 2) gemcitabine/cisplatin, which was also assessed in phase 2 studies (median survival = 9.6–11.2 months).[195-197] Gemcitabine/cisplatin may be useful for patients who cannot take pemetrexed. A comparison of 1704 patients with medically inoperable MPM treated with cisplatin/pemetrexed or carboplatin/pemetrexed as part of an expanded access trial found that outcomes with the regimens were similar.[198] Recently, the NCCN Panel deleted the caveat that carboplatin/pemetrexed regimen is a better choice for patients with poor PS and/or comorbidities, because panel members feel this regimen can also be used for patients with good PS based on clinical trial data.[198]

A phase 2 trial assessed adding bevacizumab to carboplatin/pemetrexed with or without maintenance bevacizumab as first-line therapy for patients with unresectable MPM.[199] Overall survival was 15.3 months; 34% (26/76) of patients had a partial response and 58% (44/76) had stable disease. Bowel perforation occurred in 4% of patients, and grade 3 to 4 fatigue occurred in 8%; there were 3 toxic deaths. Maintenance bevacizumab (maximum, 1 year) was administered to patients without progression and/or severe toxicities. The NCCN Panel recommends (category 2A) adding bevacizumab to carboplatin/pemetrexed with or without maintenance bevacizumab as a first-line therapy option for patients with unresectable MPM based on this trial. Acceptable first-line single-agent options include pemetrexed or vinorelbine for patients who are not candidates for platinum-based combination therapy.[200-202]

Subsequent Systemic Therapy

Limited data are available to guide second-line and beyond (subsequent) chemotherapy.[186,203-206] Recent data suggest that immune checkpoint inhibitors—pembrolizumab or nivolumab with (or without) ipilimumab—may be useful as subsequent systemic therapy for patients with MPM.[207-217] Response rates have been low with subsequent chemotherapy (7%–20%), although they are slightly higher with the new immunotherapy regimens.[207-209,218,219] Human immune checkpoint inhibitor antibodies, such as pembrolizumab and nivolumab, inhibit the programmed death-1 (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T cells.[220] Nivolumab and pembrolizumab inhibit PD-1 receptors.[220] Testing for PD-L1 is not required for prescribing pembrolizumab or nivolumab for subsequent therapy for patients with MPM. Ipilimumab is a monoclonal antibody that inhibits cytotoxic T-lymphocyte protein 4 (CTLA-4), which is another immune checkpoint; inhibition of CTLA-4 improves T-cell activity, thus increasing the anti-tumor immune response.

Immune-related adverse events, such as pneumonitis, may occur with nivolumab with (or without) ipilimumab or pembrolizumab (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[221-223] Intravenous high-dose corticosteroids should be administered based on the severity of the

reaction for patients with immune-mediated adverse events. Nivolumab with (or without) ipilimumab or pembrolizumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). Ipilimumab can also cause immune-mediated adverse events such as hepatitis and endocrinopathies.

Trial Data

A phase 2 randomized trial (IFCT-1501 MAPS2; n = 125) assessed nivolumab with (or without) ipilimumab as subsequent therapy for patients with MPM.[207,212,213] Updated results from this trial indicate that median overall survival was 15.9 months (95% CI, 10.7–not reached) in the nivolumab/ipilimumab arm and 11.9 months (95% CI, 6.7–17.7) with nivolumab alone.[207,213] The 12-month overall survival rates were 58% with the nivolumab/ipilimumab arm and 49% with the nivolumab alone. The overall response rate was 28% (95% CI, 16%–40%) with nivolumab/ipilimumab versus 19% (95% CI, 8%–29%) with nivolumab alone. The disease control rate at 12 weeks was 52% (32/62) for nivolumab/ipilimumab versus 40% (25/63) for nivolumab alone.[207] Positive PD-L1 levels were associated with overall response rate, especially high PD-L1 levels of 25% or more. However, only a few patients had very high PD-L1 expression levels of 50% or more. There were more grade 3 to 4 adverse events in the nivolumab/ipilimumab arm when compared with the nivolumab alone arm (26% vs. 14%) based on updated data; 3 treatment-related deaths were reported in the nivolumab/ipilimumab arm (one each: metabolic encephalopathy, fulminant hepatitis, and acute renal failure).[207] A phase 2 Dutch trial (INITIATE) assessed nivolumab/ipilimumab as subsequent therapy in patients with MPM.[208] Results showed a disease control rate of 68% at 12 weeks (23/34; 95% CI, 50%–83%); 29% (10/34) had a partial response and 38% (13/34) of patients had stable disease.[208] Grade 3 treatment-related adverse events were reported in 34% (12/35) patients; 94% (33/34) of patients had treatment-related adverse events.

A phase 2 trial assessed nivolumab alone as subsequent therapy in patients with recurrent MPM.[224] Of 34 patients, 13 patients benefited from nivolumab (39%; 9 with partial response and 4 with long-term stable disease [tumor was stable for more than 6 months]). Of the 9 patients with a partial response, 2 had to stop nivolumab due to pneumonitis. Median overall survival was 11.8 months (95% CI, 9.7–15.7). The objective response rate was 26%. PD-L1 expression was measured in 26% of patients (9/34) but was not associated with outcome. Grade 3 to 4 adverse events occurred in 26% of patients (9/34); one patient died of treatment-related pneumonitis. A phase 1b trial (KEYNOTE-028) is assessing pembrolizumab as subsequent therapy for 25 patients with PD-L1–positive MPM (>1% PD-L1 expression levels). Preliminary data indicate a partial response rate of 20% (5/25) (95% CI, 6.8–40.7); 52% (13/25) of patients had stable disease.[210] The median response duration was 1 year (95% CI, 3.7 months–not reached). Grade 3 adverse events were reported in 20% (5/25) of patients. Updated results from this trial indicate a median overall survival of 18 months (95% CI, 9.4–not reached); the 12-month overall survival rate was 62.6%.[211] The overall response rate was 28% (7/25); 48% (12/25) of patients had stable disease. Grade 3 to 4 drug-related adverse events occurred in 5 (20%) patients. No treatment-related deaths or need for discontinuing pembrolizumab have been reported in the KEYNOTE-028 trial.

A phase 2 trial in 34 patients is assessing pembrolizumab as subsequent therapy for patients with MPM or peritoneal mesothelioma; patients were not selected for PD-L1 expression.[58] Preliminary data indicate a median progression-free survival (PFS) of 6.2 months (95% CI, 3.2–8.2); the median overall survival has not been reached. A partial

response occurred in 21% (7/34) of patients, stable disease in 56% (19/34), and progression in 18% (6/34). Response did not correlate with PD-L1 expression. Early death occurred in 6% (2/34) of patients; grade 5 toxicity included autoimmune hepatitis (3%) and unknown (3%). Grade 3 to 4 toxicity included pneumonitis (6%), fatigue (6%), adrenal insufficiency (6%), colitis (3%), confusion (3%), hyponatremia (3%), and neutropenia (3%).

Another phase 2 trial assessed pembrolizumab as second-line monotherapy in 48 patients with MPM.[209] The overall response rate was 37% in patients with a PS of 0 to 1; high and intermediate PD-L1 expression were associated with an improved response rate when compared with negative PD-L1 expression (44% vs. 42% vs. 11%; *P*=.01). Most patients were negative for PD-L1 expression; only 14% of patients had high PD-L1 expression. The median overall survival was 10.2 months.

NCCN Recommendations

Based on these trials, the NCCN Panel recommends the following subsequent immunotherapy options for patients with MPM: 1) pembrolizumab monotherapy (category 2A); or 2) nivolumab with (or without) ipilimumab (category 2A).[58,210-213] For the 2019 update, the NCCN Panel revised the recommendation for nivolumab with (or without) ipilimumab to category 2A (from category 2B) based on recent clinical trial data.[207,208,224] The NCCN Panel also recommends subsequent chemotherapy options including pemetrexed (if not administered first line) (category 1), vinorelbine, or gemcitabine.[201,203,225-230] Data suggest that rechallenging with pemetrexed is effective if patients had a good response to first-line pemetrexed.[203,219]

Radiation Therapy

It is very challenging to accurately and safely deliver RT to the entire pleural surface without damaging radiosensitive sites, such as the lung and heart, especially when the lungs are intact.[231] The *Principles of Radiation Therapy* for MPM are described in the algorithm and are summarized in this Discussion (see the algorithm). The NCCN Guidelines for Non-Small Cell Lung Cancer are also a useful resource (see *Principles of Radiation Therapy*). In patients with MPM, RT can be used as part of a multimodality regimen; however, RT alone is not recommended for treatment. RT can also be used as palliative therapy for relief of chest pain, bronchial or esophageal obstruction, or other symptomatic sites associated with MPM, such as metastases in bone or in the brain (see the algorithm and NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[25,120,232] The dose of radiation should be based on the purpose of treatment.[233] The most appropriate timing of delivering RT (ie, after surgical intervention, with [or without] chemotherapy) should be discussed with a multidisciplinary team. After EPP, adjuvant RT may reduce the local recurrence rate.[234-237] Patients are candidates for RT if they have good PS, pulmonary function, and kidney function (see *Principles of Radiation Therapy* in the algorithm). In patients with limited or no resection of disease (ie, in the setting of an intact lung), high-dose conventional RT to the entire hemithorax has not been shown to improve survival and is associated with significant toxicity.[120,238]

A phase 2 trial (IMPRINT) (n = 27) evaluated the safety of hemithoracic intensity-modulated RT (IMRT) in patients with MPM, given after induction chemotherapy and surgery.[239] Radiation pneumonitis was reported in 30% (95% CI, 14%–50%) of patients (grade 2 in 6 patients, grade 3 in 2 patients) that was reversible with corticosteroids. Most patients had stage III or IV MPM; most evaluable patients had a partial P/D. In patients with resectable tumors, 2-year overall survival was

59%. Mediastinal nodal failure occurred in 22% (6/27) of patients; distant progression occurred in 48% (13/27) of patients. Based on this trial, the NCCN Panel recommends that hemithoracic IMRT can be considered following induction chemotherapy and P/D in certain patients with MPM if done in centers with expertise in this technique.

It has been controversial whether immediate (prophylactic) RT is useful for preventing instrument-tract recurrence after pleural intervention.[240-245] An older French trial reported that prophylactic RT was useful for preventing recurrence, but 2 other trials did not find any benefit.[240,244,245] A phase 3 randomized trial (SMART trial) compared prophylactic radiotherapy with deferred radiotherapy to assess the rate of recurrences in patients who had had procedures for MPM.[246] Patients in the deferred RT arm did not receive RT until procedure-tract metastases were evident. Data showed no difference in procedure-tract recurrence in the prophylactic RT arm (9% [9/102]) versus the deferred RT arm (16% [16/101]) (odds ratio [OR], 0.51 [95% CI, 0.19–1.32]). In addition, prophylactic RT did not improve the quality of life, decrease chest pain, or decrease the need for analgesic drugs. However, if patients did not receive chemotherapy, prophylactic RT did decrease the risk for procedure-tract metastases (OR, 0.16 [95% CI, 0.02–0.93]; *P* = .021). For the 2019 update, the NCCN Panel no longer routinely recommends prophylactic RT to prevent instrument-tract recurrence after pleural intervention based on the SMART trial (see *Principles of Radiation Therapy* in the algorithm).[117,154,237,238,246-249] Several prophylactic RT dose regimens are cited in the literature.[240,244-246]

CT simulation–guided planning using either IMRT or conventional photon/electron RT is acceptable.[176,234,236,250] For treatment planning, PET scans can be used as indicated. The clinical target volumes should be reviewed with the thoracic surgeon to ensure coverage of all the volumes at risk. The total doses of radiation are described in the algorithm (see *Principles of Radiation Therapy*). For the 2019 update, the postoperative RT doses after EPP were revised to 45 to 60 Gy in 1.8 to 2 Gy, depending on the margin status. A dose of 60 Gy or more is recommended for macroscopic residual tumors, if the doses to normal adjacent structures are limited to their tolerances (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org; note that these normal dose constraints were recently revised).[114] The volume of postoperative radiation should cover the surgical bed within the thorax.[117,154,237,238,248,249] The optimal dose of RT for palliative purposes remains unclear.[233,251] For patients with chest pain from MPM, total doses of 20 to 40 Gy appear to be effective in providing relief from pain.[25,240,241]

IMRT allows a more conformal high-dose RT and improved coverage to the hemithorax at risk.[114,120,234,235,239,252-255] Advanced technologies, such as image-guided RT, may be used for treatments involving IMRT or helical tomotherapy (HT), stereotactic radiosurgery, or stereotactic body radiation therapy.[231,256] The NCI and ASTRO/ACR IMRT guidelines are recommended.[257-259] The ICRU-83 (International Commission on Radiation Units & Measurements Report 83) recommendations are also a useful resource.[260,261] RT to the contralateral lung should be minimized,[120,235,262] because fatal pneumonitis may occur with IMRT if strict limits are not applied.[263-265] The mean lung dose should be kept as low as possible, preferably less than 8.5 Gy.[266] The volume of contralateral lung receiving low-dose RT (eg, 5 Gy) should be minimized.[267,268] Hemithoracic IMRT immediately followed by EPP was assessed in 25 patients with stage III or IV MPM on final pathologic review; for patients with epithelial subtypes of MPM, 3-year survival reached 84%.[254] However, 13 patients had grade 3+ surgical complications and one patient died from treatment.

Summary

These NCCN Guidelines focus on MPM, which is the most common type of mesothelioma. This Discussion text for MPM describes the recommendations in the algorithm in greater detail, for example, by including the clinical trial data and other references that support the NCCN Panel's recommendations in the algorithm. Revisions for the 2019 update are described in this Discussion and outlined in the algorithm (see *Summary of the Guidelines Updates*). For the 2019 update (Version 1), the NCCN Guidelines now recommend that surgery should be considered for patients with clinical stage I to IIIA MPM and clarify that surgery is not an option for those with stage IIIB or IV MPM regardless of histology.[140] The NCCN Panel also revised the recommendation for subsequent therapy with nivolumab with (or without) ipilimumab to category 2A (from 2B) based on recent trial data.[207,208,224]

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