Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-164 Nivolumab

Stand: September 2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Nivolumab
in Kombination mit Ipilimumab zur Erstlinientherapie des fortgeschrittenen nicht-resezierbaren malignen Pleuramesothelioms

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	nicht zutreffend.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Beratungsanforderung/Fachinformation)
Zu bewertendes Arzneimittel:	
Nivolumab L01XC17 Opdivo®	Zugelassenes neues Anwendungsgebiet: OPDIVO ist in Kombination mit Ipilimumab für die Erstlinientherapie des fortgeschrittenen nicht-resezierbaren malignen Pleuramesothelioms bei Erwachsenen indiziert.
Pemetrexed L01BA04 Alimta®	Malignes Pleuramesotheliom ALIMTA in Kombination mit Cisplatin ist angezeigt zur Behandlung von chemonaiven Patienten mit inoperablem malignen Pleuramesotheliom. […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-164 (Nivolumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	5. August 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Kombination mit Ipilimumab für die Erstlinientherapie des fortgeschrittenen nicht-resezierbaren malignen Pleuramesothelioms bei Erwachsenen indiziert.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Pleuramesotheliom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 15.07.2019 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 291 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 5 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es wurden keine relevanten IQWiG Bericht oder G-BA Beschlüse identifiziert.

3.2 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.4 Leitlinien

National Comprehensive Cancer Network, 2019 [4].

NCCN Guideline, Version 2.2019

Malignant Pleural Mesothelioma

Leitlinienorganisation/Fragestellung

k.A.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz nicht ausreichend dargelegt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- k.A.

LoE

- k.A.

GoR

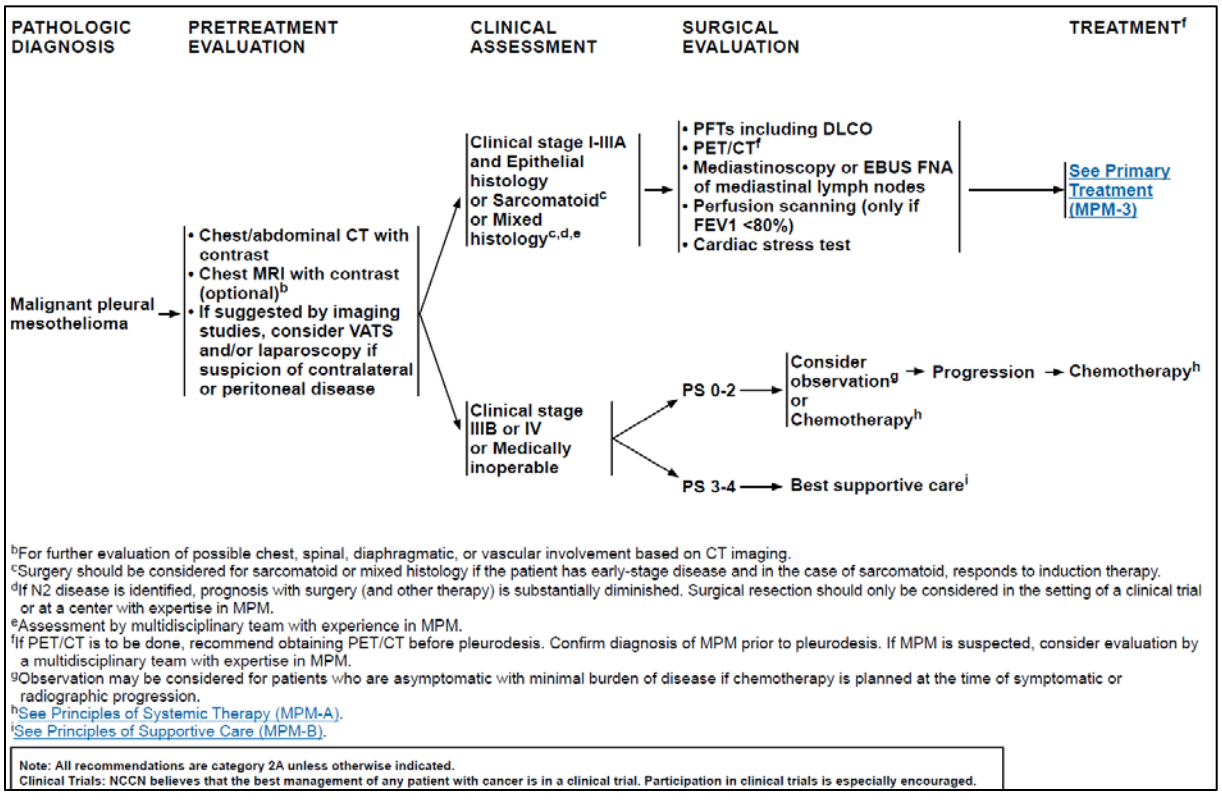
- **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
- **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

- **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.

Sonstige methodische Hinweise

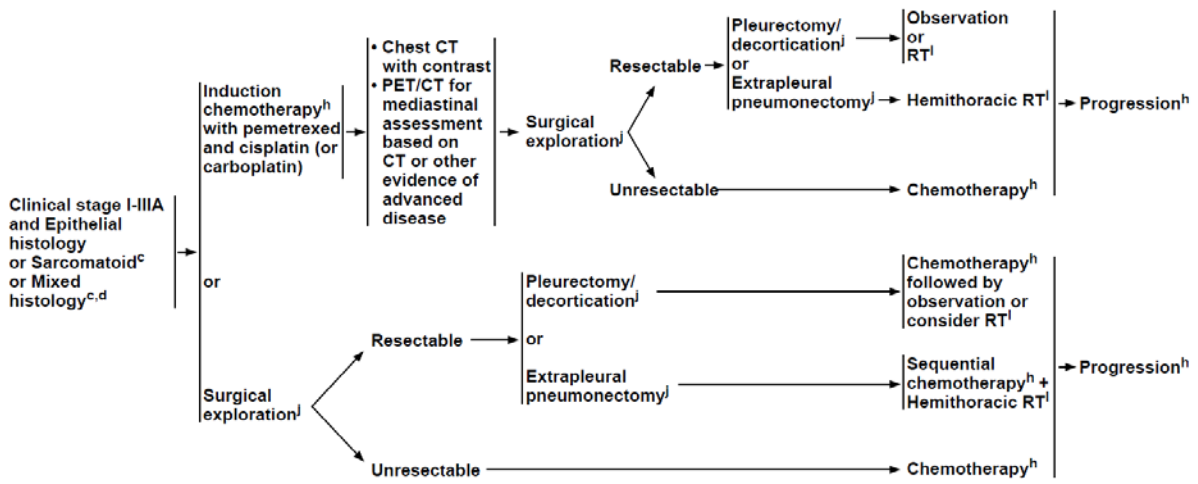
- All recommendations are category 2A unless otherwise indicated.
- Methodenreport beschreibt zwar systematische Evidenzaufbereitung mit Konsensusprozessen, ob formalisierte Konsensusverfahren angewendet werden ist jedoch unklar
- Repräsentativität der Gremien unklar
- (Eigenes Graduierungssystem)
- Industriefinanziert
- Auswahlprozess der Literatur unklar
- Keine system. Bewertung der Validität der Studien, sondern “quality of data based on trial design”

Empfehlungen



[b]For further evaluation of possible chest, spinal, diaphragmatic, or vascular involvement based on CT imaging.
[c]Surgery should be considered for sarcomatoid or mixed histology if the patient has early-stage disease and in the case of sarcomatoid, responds to induction therapy.
[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]Assessment by multidisciplinary team with experience in MPM.
[f]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.
[g]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.
[h]See Principles of Systemic Therapy (MPM-A).
[i]See Principles of Supportive Care (MPM-B).

Note: 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.



[c]Surgery should be considered for sarcomatoid or mixed histology if the patient has early-stage disease and in the case of sarcomatoid, responds to induction therapy.
[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.
[h]See Principles of Systemic Therapy (MPM-A).
[i]See Principles of Supportive Care (MPM-B).
[j]See Principles of Surgery (MPM-C).
[k]See NCCN Guidelines for Survivorship.
[l]See Principles of Radiation Therapy (MPM-D).

Note: 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.

PRINCIPLES OF SYSTEMIC THERAPY

FIRST-LINE CHEMOTHERAPY REGIMENS

- Pemetrexed* 500 mg/m² day 1
  Cisplatin 75 mg/m² day 1
  Administered every 3 weeks (category 1)[1]
- Pemetrexed* 500 mg/m² day 1
  Cisplatin 75 mg/m² day 1
  Bevacizumab 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,**]
- Pemetrexed* 500 mg/m² day 1
  Carboplatin AUC 5 day 1[3-5]
  ± bevacizumab 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**
- 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* 500 mg/m² every 3 weeks[9]
- Vinorelbine 25–30 mg/m² weekly[10]

SUBSEQUENT SYSTEMIC THERAPY

- Pemetrexed* (if not administered as first-line) (category 1)[11]
  Consider rechallenge if good sustained response at the time initial chemotherapy was interrupted[12]
- Vinorelbine[13,14]
- Gemcitabine[14-16]
- Nivolumab ± ipilimumab[17-19]
- Pembrolizumab[20,21]

*Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma.[22]
**The combination regimen of pemetrexed/cisplatin/bevacizumab or pemetrexed/carboplatin/bevacizumab is only for unresectable disease.

Note: 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.

MPM

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]

Referenzen:

PRINCIPLES OF SYSTEMIC THERAPY
REFERENCES

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British Thoracic Society

British Thoracic Society Guideline for the investigation and management of malignant pleural mesothelioma

Leitlinienorganisation/Fragestellung

The key aim of this guideline is to provide detailed, evidence-based guidance for the investigation of suspected MPM and the subsequent care and management of individuals with proven MPM. MPM is a rare cancer where the malignancy affects the pleura, a thin membrane of lubricating cells that lines the lungs and chest wall.

Relevant key questions:

- Is there a role for systemic anticancer treatment in MPM?
- Is there a role for radiotherapy in MPM?

Methodik

Grundlage der Leitlinie

Systematische Literaturrecherche und Evidenzaufbereitung; The full GDG reviewed each section during the regular meetings and consensus was reached.

Recherche/Suchzeitraum:

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;

- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and MEDLINE In-Process, EMBASE and PUBMED till December 2014

LoE und GoR

LoE

Table 1 SIGN levels of evidence

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort or studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg, case reports, case series
4	Expert opinion

GoR

Table 2 SIGN grades of recommendations

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+
√	*Good practice points* Recommended best practice based on the clinical experience of the guideline development group

Sonstige methodische Hinweise

- Stakeholders were identified at the start of the process and where appropriate societies and organisations were contacted and asked to nominate a specific person to join the GDG. All stakeholder organisations were notified when the guideline was available for public consultation.
- BTS Declarations of Interest forms have been completed by all members for each year they were part of the GDG. Details of these forms can be obtained from BTS Head Office. Declarations of Interest was a standing item at each GDG meeting.
- In line with BTS policy, this guideline will be reviewed by the SOCC within 5 years of publication.

Empfehlungen

Systemic anticancer treatment

Recommendations

- Offer patients with MPM with good PS (WHO 0–1) first-line therapy with cisplatin and pemetrexed. Where licensed (not presently in the UK), bevacizumab should be added to this regime. Raltitrexed is an alternative to permetrexed. Grade A.

Evidence statements

- For patients with MPM with good PS, first-line chemotherapy with cisplatin and pemetrexed leads to longer survival than cisplatin alone. Evidence level 1 + +.

- For patients with MPM with good PS, first-line therapy with cisplatin and pemetrexed and bevacizumab leads to longer survival than cisplatin and pemetrexed alone. Evidence level 1 + +.
- For patients with MPM with good PS, first-line chemotherapy with cisplatin and raltitrexed leads to longer survival than cisplatin alone. Evidence level 1 + +.
- The combination of mitomycin, cisplatin and vinblastine or single agent vinorelbine did not demonstrate survival benefit over active symptom control. Evidence level 1 +.
- Carboplatin in combination with pemetrexed is a safe and effective alternative to cisplatin in combination with pemetrexed. Evidence level 3.

Good practice points

- Where cisplatin is contraindicated, or has adverse risk, offer carboplatin in combination with pemetrexed.

Research recommendations

- The role of immunotherapy in MPM should be further assessed in large phase III RCTs.

Buikhuisen *et al* undertook a systematic review of 10 studies reporting on 1251 patients treated with second-line chemotherapy in MPM.[121] The majority of studies were phase II with only two phase III randomised trials. The authors concluded that only a limited number of randomised studies with combination therapy had been conducted. The authors suggested the following as second-line treatment options for patients with MPM: 'single agent vinorelbine or pemetrexed are acceptable second-line agents for patients relapsing after a first-line platinum combination regardless of whether or not pemetrexed was used in the first-line setting'. They also stated that the 'low reported activity of the drugs in second line warrants referral of fit patients to participate in clinical trials'. Jassem et al compared the efficacy and safety of pemetrexed and best supportive care in patients with MPM after first-line chemotherapy (excluding pemetrexed).122 Of the 243 patients included, 18.7% of the 143 patients receiving pemetrexed showed a partial response but the median overall survival was not significantly different between the two groups.

The VANTAGE-014 study compared vorinostat, an oral histone deacetylase inhibitor, with placebo in 661 patients with MPM who had previously received one or two systemic regimens.[123] Median overall survival for vorinostat was 30.7 weeks (95% CI 26.7 to 36.1) vs 27.1 weeks (95% CI 23.1 to 31.9) for placebo (HR 0.98, 95% CI 0.83 to 1.17, P=0.86). Anti-PD1 immune checkpoint therapy has potential for the treatment of mesothelioma. Approximately 40% of tumours express PDL1, which is associated with non-epithelioid histology and worse outcome for high expressing tumours.124 Keynote 28 is the first phase Ib trial to report on the activity of pembrolizumab in patients with pleural mesothelioma and enrolled 25 patients harbouring PDL1-positive tumours.125 This study showed a 20% response rate with durability lasting on average 12 months. Stable disease was 52% giving a disease control rate of 72%. Median overall survival was 18 months. In summary, emerging data suggest anti-PD1 or PDL1 immunotherapy, exhibits efficacy in mesothelioma; however, randomised trials will be needed to confirm the incremental benefit and value. In this regard, the CRUK CONFIRM phase III trial is currently randomising patients 2:1 to nivolumab versus placebo (NCT03063450).

Radiotherapy

Prophylactic radiotherapy to procedure tracts

Recommendation

- Do not offer prophylactic radiotherapy to chest wall procedure tracts routinely. Grade A.

Evidence statements

- Three out of four RCTs did not show a reduction in procedure tract metastases with prophylactic radiotherapy to chest wall procedure tracts. Level 1+.
- Prophylactic radiotherapy to chest wall procedure tract has not been shown to improve quality of life, chest pain, analgesia requirements or survival. Level 1+.

Four RCTs comparing prophylactic radiotherapy to procedure tracts to no radiotherapy, and a systematic review (written before the 2016 RCT was published) are evaluated.126–130 The study by Boutin et al was conducted in the era before chemotherapy was routinely offered to patients with MPM fit enough to receiveit.126 All patients had both an Abrams biopsy and a thoracoscopy before randomisation. The incidence of metastatic nodules in the control group was high (40%) and has not been replicated in any other observational studies. The studies by Bydder et al and O'Rourke et al excluded patients who had received prior chemotherapy.127 128 Information regarding subsequent chemotherapy treatment was not available. The incidence of chest wall nodules in the control groups were lower and the differences in the incidence of

nodules between treatment groups not significantly different. It has been questioned whether these studies were adequately powered.130

The SMART trial was a randomised, multicentre, phase III trial evaluating whether prophylactic radiotherapy reduces the incidence of procedure tract metastases after surgical and large bore pleural procedures.129 Eligible patients were recruited from 22 UK hospitals and randomised (1:1) to immediate radiotherapy (21 Gy in three fractions over three working days), or deferred radiotherapy (same dose given if a procedure tract metastasis (PTM) developed). Two hundred three patients were randomised (102 to immediate radiotherapy, 101 to deferred radiotherapy). No statistically significant difference was identified in the PTM rates of the immediate and deferred radiotherapy groups (9/102 (8.8%) vs 16/101 (15.8%), respectively; OR 0.51, 95% CI 0.19 to 1.32; P=0.14). There was no difference identified in quality of life, chest pain, analgesia requirements or survival of the two groups.

A Phase III Randomised Trial of Prophylactic Irradiation of Tracts in Patients with Malignant Pleural Mesothelioma Following Invasive Chest Wall Intervention (the PIT trial) was due to complete recruitment in June 2016 and results are expected in 2017.131 Table 16 provides a summary of trials comparing prophylactic and procedure tracts with no radiotherapy.

Table 16 Summary of trials comparing prophylactic radiotherapy to procedure tracts to no radiotherapy

Study	Patients	Treatments	Nodules in treatment group	Nodules in control group	Significance	Notes
Boutin 1995[126]	40	21 Gy in 3 12.5–15 MeV	0/20	8/20	P<0.001	Prechemotherapy era
Bydder 2004[127]	43 (58 sites)	10 Gy in 19 MeV	2/28	3/30	N.S.	Chemotherapy patients excluded
O'Rouke 2007[128]	61	21 Gy in 3 250 kV photons or 9–12 MeV	4/31	3/30	N.S.	Chemotherapy patients excluded
Clive 2016[129]	203	21 Gy in three fractions	9/102	16/101	N.S.	Chemotherapy included

N.S., not significant

Radiotherapy as part of multimodality treatment

Recommendation

- Do not offer preoperative or postoperative radiotherapy in MPM. Grade A.

Evidence statements

- *Postoperative radiotherapy after chemotherapy and EPP has not been shown to improve survival. Level 1+.*
- *Postoperative radiotherapy after chemotherapy and pleurectomy decortication has not been shown to improve survival. Level 2−.*
- *Preoperative radiotherapy has not been shown to improve survival. Level 2−.*
- *Radical radiotherapy used in isolation has not been shown to improve survival. Level 2−.*

Research recommendation

- Prospective clinical trials of preoperative radiotherapy, postoperative radiotherapy after pleurectomy decortication and definitive radiotherapy after chemotherapy in MPM are required.

Twenty-one studies were identified which included radiotherapy as part of the multimodality treatment.103 132–151 One evaluated preoperative radiotherapy (in the context of EPP),132 2 hemithoracic radiotherapy alone133 134 and 17 postoperative radiotherapy (4 in the context of pleurectomy decortication and 13 in the context of EPP).

Four studies were retrospective cohort series and 16 were prospective studies, of which only 4 are multicentre and 2 are RCTs. Studies evaluating postoperative radiotherapy either after EPP or PD have shown that radiotherapy in the context of multimodality treatment is feasible, but some severe toxicities, particularly pneumonitis have been reported.103 135–150 The rate of grade 5 radiation pneumonitis ranges from 0% to 46% in the studies that have reported radiotherapy-related toxicity and a lung dose-volume effect was identified in patients who developed grade 3+ radiation pneumonitis.135 140 142–144 Only one RCT specifically evaluated the role of postoperative radiotherapy and showed no benefit for this treatment.150

The Swiss Group for Clinical Cancer Research (SAKK) trial is a two-part multicentre randomised phase II study, analysed on intention to treat. It included patients with pathologically confirmed MPM, resectable TNM stages T1–3 N0–2, M0, WHO PS 0–1 and age <70 years. In part 1 of the study, patients were given three cycles of neoadjuvant chemotherapy followed by EPP; the primary end point was complete macroscopic resection (R0–1). In part 2, patients with complete macroscopic resection were randomly assigned to receive adjuvant radiotherapy or not (three-dimensional conformal radiotherapy or

intensity-modulated radiotherapy was permitted with dose ranging from 55.9 to 57.6 Gy, using a boost technique). The primary end point was locoregional relapse-free survival. One hundred fifty-one patients were evaluable after neoadjuvant chemotherapy, of whom 75% had EPP and 64% complete macroscopic resection.

Fifty-four patients were enrolled in part 2. Median locoregional relapse-free survival from surgery was 7.6 months (95% CI 4.5 to 10.7) in the no radiotherapy group and 9.4 months (95% CI 6.5 to 11.9) in the radiotherapy group. Median overall survival calculated from registration for patients in part 2 was 20.8 months (95% CI 14.4 to 27.8) in the no radiotherapy group and 19.3 months (95% CI 11.5 to 21.8) in the radiotherapy group. One patient died of grade 5 radiation pneumonitis. However, it should be noted the trial was terminated earlier than planned due to slow accrual (at 73% of the accrual).

Radiotherapy for symptom palliation

Recommendation

- Do not offer hemithorax radiotherapy for MPM. Grade D.
- Consider palliative radiotherapy for localised pain in MPM where the pain distribution matches areas of underlying disease. Grade D.

Evidence statements

- Hemithorax radiotherapy has not been shown to have a consistent impact on chest pain or PS in MPM. Level 3.
- Localised radiotherapy can improve pain control in MPM, although the effect is variable and is short lived. Level 3.
- Radiation dose fractionation utilised in studies of localized radiotherapy for pain control in MPM are variable. The optimal dose is not known. Level 3.

Research recommendation

- Further prospective randomised clinical trials are required to determine the role of radiotherapy for symptom control in MPM and the optimal dose fractionation.

There are six studies, of which two explore whole hemithorax irradiation133 152 and four of localised treatment to areas of disease and/or symptoms.153–156 There are two systematic reviews addressing the role of radiotherapy for symptom palliation.157 158 Of the hemithorax studies, a retrospective case series described no change in chest pain or PS in 47 patients treated with 40 Gy in 20 fractions.133 The other was a prospective phase II study without controls, including 19 patients treated with 30 Gy in 10 fractions.152 It reported an improvement in pain control in 68% at 1 month, but this was not maintained (1). Toxicity was not reported in this study. The localised treatment studies showed variable response rates (in terms of pain improvement). The dose and duration of response were also variable in these uncontrolled reports. The results are summarised in table 17. A randomised phase II study opened to recruitment in the UK in August 2016 aiming to establish optimal dose/fractionation for symptom control in MPM (SYSTEMS2 SRCTN12698107).

Table 17 Summary of studies exploring localised hemithorax irradiation

Study	Type of study	Patients	Dose; number of fractions (#)	Pain improvement %	Duration of response
Macleod[153]	Prospective phase II No control	40	20 Gy; 5#	47	5 weeks
Davis[154]	Retrospective	111	<20 Gy* >40 Gy*	60 57	No data
Graaf-Strukowska[155]	Retrospective	189	<4 Gy; 1# 36 Gy; 9#	40 50	98 days 69 days
Jenkins[156]	Retrospective	54	36 Gy; 12#	57	2 weeks

* Fractionation not specified.

Kindler HL et al., 2018 [2].

American Society of Clinical Oncology

Treatment of Malignant Pleural Mesothelioma: American Society of Clinical Oncology Clinical Practice Guideline

Siehe auch: Kindler HL et al., 2018 [3].

Leitlinienorganisation/Fragestellung

To provide evidence-based recommendations to practicing physicians and others on the management of malignant pleural mesothelioma.

Relevant key questions:

- What is the appropriate first- and second-line systemic treatment of patients with mesothelioma?
- When should radiation be recommended for mesothelioma?
- What is the optimal duration of front-line chemotherapy for mesothelioma? Is there a role for pemetrexed maintenance therapy in pleural mesothelioma?

Methodik

Grundlage der Leitlinie

Systematische Literaturrecherche und Evidenzaufbereitung; multidisziplinäres Expertenpanel; externer Review der Leitlinie; formeller oder informeller Konsensus (siehe sonstige methodische Hinweise)

Recherche/Suchzeitraum:

- PubMed and the Cochrane Collaboration Library till May 2017

LoE & GoR

LoE

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits *v* harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

GoR

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of Expert Panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Sonstige methodische Hinweise

- Strukturierter Prozess zur Aktualisierung der Leitlinie
- In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.
- Type of recommendation:

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Expert Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Expert Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Expert Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Expert Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Empfehlungen

Chemotherapy

In patients with newly diagnosed pleural mesothelioma, is there a role for chemotherapy and does it improve survival and QoL? (a) Who should receive supportive care instead of chemotherapy? (b) Is there a role for additional modalities in these patients?

- Recommendation 1.1.: Chemotherapy should be offered to patients with mesothelioma because it improves survival and QoL (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Recommendation 1.2.: In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be offered prior to the initiation of chemotherapy (Type of recommendation: informal consensus; Strength of recommendation: moderate).
- Recommendation 1.3.: Selected patients with a poor performance status (PS 2) may be offered single-agent chemotherapy or palliative care alone. Patients with a PS of 3 or greater should receive palliative care (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation.

Chemotherapy improves survival and QoL in previously untreated patients with MPM. In the pivotal study by Vogelzang et al,1 the combination of pemetrexed plus cisplatin improved the response rate, progressionfree and overall survival compared with cisplatin alone. Using the Lung Cancer Symptom Scale instrument to evaluate QoL, the trial demonstrated statistically significant improvements in dyspnea and pain with combination chemotherapy. A similar study with raltitrexed/cisplatin showed that doublet chemotherapy improved overall survival compared with cisplatin alone. Global health-related QoL (HRQoL) was comparable on both arms (P = .848), and both treatments yielded improvements in dyspnea. Few clinically significant differences between treatment arms were observed using the European Organisation

for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) or Lung Cancer 13.10,17 In the MAPS (Mesothelioma Avastin Cisplatin Pemetrexed Study) trial, the addition of bevacizumab to standard pemetrexed/cisplatin chemotherapy improved progression-free and overall survival. Chemotherapy improved QoL above baseline in both arms.20 The MS01 phase III trial compared active symptom control (ASC) to mitomycin/vinblastine/cisplatin or vinorelbine in 409 previously untreated patients with MPM. Median overall survival was 7.6 months for ASC and 8.5 months for the combined chemotherapy arms, which was not statistically significant (HR, 0.89; P = .29). There were no differences in the QoL subscales of physical functioning, pain, dyspnea, and global health status between arms.

Exploratory analyses suggested a survival advantage for vinorelbine compared with ASC alone, which did not reach statistical significance since the study was underpowered (HR, 0.80; P = .08).6 Epithelial MPM can sometimes be quite indolent. In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be offered prior to the initiation of chemotherapy. A 43-patient randomized trial compared immediate chemotherapy with mitomycin/ vinblastine/cisplatin to chemotherapy at the time of symptomatic progression. Early chemotherapy provided an extended period of symptomcontrol and a trend toward a survival improvement that was not statistically significant.18 The SWAMP (South West Area Mesothelioma and Pemetrexed) trial assessed HRQoL using the EQ-5D, European Organisation for Research and Treatment of Cancer QLQC30, and LC-13 in 73 consecutive patients who were fit for first-line pemetrexed/platin chemotherapy; 58 patients received chemotherapy and 15 chose best supportive care (BSC). Patients who received chemotherapy maintained their QoL better than the BSC group (P = .006); the latter experienced a decline in their HRQoL, with worse dyspnea and pain. Patients receiving chemotherapy who had radiographic improvement or a decline in serum mesothelin also had a better HRQoL at 16 weeks.88 It is reasonable to offer selected patients with PS 2 single-agent chemotherapy with pemetrexed,126,129 vinorelbine,6 or gemcitabine. 180 Response rates are expected to be quite low. Patients with a PS of 3 or greater should receive palliative care.

<u>What is the best chemotherapy regimen for patients with newly diagnosed pleural mesothelioma who are not candidates for surgery?</u>

- Recommendation 2.0.: The recommended first-line chemotherapy for patients with mesothelioma is pemetrexed plus platinum. However, patients should also be offered the option of entering in a clinical trial (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: strong).
- Literature review and clinical interpretation: It is recommended that the triplet regimen of bevacizumab, pemetrexed, and cisplatin may be offered to patients with no contraindications to bevacizumab. Given the high frequency of cardiovascular comorbidity and hypertension among patients with MPM, however, it is important to carefully select patients who might benefit from the addition of bevacizumab to chemotherapy.

<u>Literature review and clinical interpretation.</u>

Systemic chemotherapy consisting of a platinum plus pemetrexed with folic acid and vitamin B12 supplementation is the recommended first-line systemic therapy for patients with MPM with a good (# 2) performance status. The trial that led to US Food and Drug Administration approval of this regimen in MPM was a single-blind, placebo-controlled randomized phase III trial that compared cisplatin (75 mg/m2) with or without pemetrexed (500 mg/m2) in 456 previously untreated patients with MPM. The combination achieved a superiormedian overall survival (12.1 v 9.3months; P = .020; HR, 0.77) and progression-free survival (5.7 v 3.7months; P = .001) and a higher response rate (41.3% v 16.7%; P , .001) when compared with single-agent cisplatin. Vitamin supplementation was instituted after the first 117 patients enrolled, resulting in a significant reduction in toxicity without impairing survival. Toxicity was, of course, greater with the combination, producing grade 3/4 neutropenia, leukopenia, and nausea in 27.9%, 17.7%, and 14.6% of patients, respectively.

A phase III trial that compared the antifolate raltitrexed (80 mg/m2) plus cisplatin (80 mg/m2) to cisplatin alone in 250 patients similarly demonstrated higher response rates (23.6% v 13.6%) and a superior median overall (11.4 v 8.8 months) and 1-year survival (46% v 40%), for the antifolate/platinum combination compared with cisplatin alone. In this study there was no difference in HRQoL between the two arms.10,17

<u>What is the role of adding bevacizumab to the chemotherapy regimen of pemetrexed and cisplatin? Are there patients with mesothelioma who should not get bevacizumab?</u>

- Recommendation 3.1.: The addition of bevacizumab to pemetrexed-based chemotherapy improves survival in select patients and therefore may be offered to patients with no contraindications to bevacizumab. The randomized clinical trial demonstrating benefit with bevacizumab used cisplatin/pemetrexed; data with carboplatin/pemetrexed plus bevacizumab are insufficient for a clear recommendation

(Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate).

- Recommendation 3.2.: Bevacizumab is not recommended for patients with PS ≥ 2, substantial cardiovascular comorbidity, uncontrolled hypertension, age > 75, bleeding or clotting risk, or other contraindications to bevacizumab (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and clinical interpretation.

MAPS, an openlabel randomized phase III trial in 448 patients with MPM compared standard pemetrexed/cisplatin with or without the addition of bevacizumab, 15 mg/kg every 21 days.20 Eligible patients were age 75 years or younger, with no cardiovascular comorbidity or uncontrolled hypertension, who were not receiving antiaggregant, antivitamin K, low-molecular-weight heparin, or nonsteroidal agents. The three-drug combination produced a longer median overall survival compared with pemetrexed/ cisplatin (18.8 v 16.1 months; P = .0167; HR, 0.77). The superior overall survival in the control arm (which was 12.1 months in the Vogelzang et al1 trial) was attributed in part to the rigorous eligibility criteria for bevacizumab treatment. Progression-free survival was also superior with the triplet (9.2 v 7.3 months; P , .001; HR, 0.61).

As expected, the addition of bevacizumab increased the rate of grade 3/4 toxicity (71% v 62%) especially hypertension (25% v 0%) and thrombosis (6% v 1%); grade 1/2 epistaxis was also more frequent (37.4% v 6.3%).More patients stopped treatment because of toxic effects in the bevacizumab arm than in the control group (24.3% v 6%; P , .001). There was no detriment to QoL with the addition of bevacizumab. On the basis of these data, it is recommended that the triplet regimen of bevacizumab, pemetrexed, and cisplatin may be offered to patients with no contraindications to bevacizumab. Given the high frequency of cardiovascular comorbidity and hypertension among patients with MPM, however, it is important to carefully select patients who might benefit from the addition of bevacizumab to chemotherapy.

The data for bevacizumab with carboplatin/pemetrexed are insufficient for a clear recommendation. A phase II trial of pemetrexed, carboplatin (AUC 5), plus bevacizumab in 76 previously untreated patients with MPM achieved a partial response rate of 34.2%, with manageable toxicity. The median progression-free and overall survivalwas 6.9 and 15.3 months, respectively.184 There are no randomized data for this combination.

When should carboplatin be used instead of cisplatin in patients with pleural mesothelioma?

- Recommendation 4.0. In patients who may not be able to tolerate cisplatin, it is recommended that carboplatin may be offered as a substitute for cisplatin (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation.

Carboplatin is generally better tolerated and easier to administer than cisplatin. Although no randomized studies in MPM directly compare carboplatin to cisplatin, data from multiple phase II series and the pemetrexed Expanded Access Program suggest that they are likely equivalent in this disease. In phase II studies,174,176,185 carboplatin (AUC 5) combined with pemetrexed achieved response rates ranging from 19% to 29%, median progression-free survival of 7 to 8 months, and median overall survival of 13 to 14 months,46,185 similar to the pivotal phase III trial of cisplatin and pemetrexed.1 In a retrospective pooled analysis, patients.70 years of age who were treated with pemetrexed and carboplatin achieved similar outcomes as their younger counterparts, though they experienced more frequent hematologic toxicity.46

Among 1,704 previously untreated patients with MPM in the international Expanded Access Program, comparable response rates (26.3% v 21.7%), time to progression (7 v 6.9 months) and 1-year survival (63.1 v 64%) were reported for treatment with pemetrexed plus cisplatin or carboplatin, respectively. Grade 3/4 neutropenia was greater in patients who received pemetrexed plus carboplatin than pemetrexed plus cisplatin: 36.1% v 23.9%, respectively.127 Based on the available nonrandomized data, substituting carboplatin for cisplatin is an acceptable first-line option for patients with unresectable MPM.

What is the most effective second-line therapy for patients with pleural mesothelioma? Can patients who have previously received pemetrexed be treated again with pemetrexed?

- Recommendation 5.1. Retreatment with pemetrexed-based chemotherapy may be offered in pleural mesothelioma patients who achieved durable (. 6 months) disease control with first-line pemetrexed-based chemotherapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

- Recommendation 5.2. Given the very limited activity of second-line chemotherapy in patients with mesothelioma, participation in clinical trials is recommended (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).
- Recommendation 5.3. In patients for whom clinical trials are not an option, vinorelbine may be offered as second-line therapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).

Literature review and clinical interpretation.

There are few active treatment options for previously treated patients with MPM. A phase III trial in 243 patients who had not received prior pemetrexed demonstrated higher response rates (18.7% v 1.7%; P , .001), superior disease control (59.3% v 19.2%; P , .0001), and longer progression-free survival (3.6 v 1.5 months; P = .0148) in those who received single-agent pemetrexed compared with BSC. This did not translate into an improvement in overall survival, however (8.4 v 9.7 months; P = .74) due to the greater use of subsequent chemotherapy in the BSC arm.7 Retreatment with pemetrexed-based chemotherapy is a reasonable option for patients who achieve durable disease control with first-line pemetrexed-based chemotherapy. A single-center retrospective review reported an overall response rate of 19% and a disease control rate of 48% among 31 patients who achieved disease control with front-line pemetrexed-based chemotherapy for at least 3 months and were then retreated with pemetrexed, alone or with a platinum.184 A multi-institution retrospective analysis of 30 patients documented a 66% disease control rate and decreased pain when patients who had at least 6 months of disease control with front-line pemetrexed/platin were rechallenged with a pemetrexed-based regimen. Time to progression was 5.1 months, and median overall survival was 13.6 months.41 A multicentre retrospective analysis showed that patients with MPM who experienced a time to progression of at least 12 months after first-line therapy had a greater likelihood of disease control with pemetrexed-based rechallenge.28

Vinorelbine is widely used as a second-line therapy in MPM, though there are limited data to support its efficacy. A single-center phase II trial of vinorelbine in 63 patients achieved a response rate of 16% and a median overall survival of 9.6 months. Similarly, a single-center retrospective review in 59 patients reported a 15% response rate and a disease control rate of 49%.233 In contrast, a retrospective review of 60 patients who received either vinorelbine or gemcitabine in the second- or third-line setting documented infrequent responses (none for vinorelbine and 2% for gemcitabine). Median progression-free survival was 1.7 and 1.6 months for vinorelbine and gemcitabine, respectively.60 Given the paucity of active agents in this setting, participation in clinical trials is highly recommended.

What is the optimal duration of front-line chemotherapy for mesothelioma? Is there a role for pemetrexed maintenance therapy in pleural mesothelioma?

- Recommendation 6.1.: In select asymptomatic patients with epithelial mesothelioma and a low disease burden who are not surgical candidates, a trial of expectant observation, with close monitoring, may be offered before initiation of systemic therapy (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- Recommendation 6.2.: Front-line pemetrexed-based chemotherapy should be given for four to six cycles. For patients with stable or responding disease, a break from chemotherapy is recommended at that point (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: moderate).
- Recommendation 6.3. There is insufficient evidence to support the use of maintenance chemotherapy and thus it is not recommended (Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).
- Recommendation 6.4. There is insufficient evidence to support the use of pemetrexed maintenance in mesothelioma patients and thus it is not recommended (Type of recommendation: evidence based; Evidence quality: low; Strength of recommendation: strong).

Literature review and clinical interpretation.

In asymptomatic patients with epithelial histology and minimal pleural disease who are not surgical candidates, a trial of close observation may be considered before the initiation of chemotherapy. A small, 43-patient randomized trial that compared immediate chemotherapy to treatment when symptoms developed demonstrated that early chemotherapy provided a longer period of symptom control and a trend toward superior survival.18 Of the patients randomized to the delayed treatment group, 23% had a performance status deterioration that precluded subsequent chemotherapy.

While it is reasonable to delay chemotherapy for patients with low disease burden and few symptoms, such patients should be monitored closely to ensure timely intervention. In the pivotal study of pemetrexed/cisplatin that led to US Food and Drug Administration approval of this combination, patients received a median of six chemotherapy cycles, with a range of one to 12. The percentage of patients who completed at least four, six, or eight cycles was 71%, 53%, and 5%, respectively.1 Since patients with durable disease control with front-line chemotherapy can respond to retreatment with a pemetrexed-based regimen, a break from chemotherapy after four to six cycles of treatment is recommended.

There is insufficient evidence to support single-agent pemetrexed maintenance in MPM, and thus it is not recommended. A nonrandomized feasibility study in 27 patients demonstrated that maintenance pemetrexed was safe and that responses could be achieved after six cycles of induction chemotherapy. But the heterogeneous patient population (untreated and previously treated), the different induction regimens (pemetrexed/carboplatin or pemetrexed alone), the small number of patientswho actually received maintenance therapy (13, only eight of whom had received front-line doublet induction chemotherapy), and the nonrandomized nature of this trial preclude any conclusions about the efficacy of this approach. 234 A randomized study of maintenance pemetrexed following induction pemetrexed/platin (Cancer and Leukemia Group B 30901) closed due to poor accrual; preliminary data on this study have not yet been reported.

Radiation therapy

Should patients receive prophylactic irradiation of intervention tracts (thoracentesis, tunneled pleural catheters, thoracoscopy, and needle biopsy) to prevent tract recurrences?

- Recommendation 1.1.: Prophylactic irradiation of intervention tracts should generally not be offered patients to prevent tract recurrences (Type of recommendation: evidence based; Evidence quality: high; Strength of recommendation: moderate).

Literature review and clinical interpretation.

Two systematic reviews,204,216 four RCTs,9,11,14,21 and one retrospective study27 were identified. Most used variable radiation therapy doses, some with antiquated techniques (electrons, superficial kVs, etc), and radiation therapy was delivered at various intervals from surgical intervention. The largest retrospective study analyzed 171 patients treated with prophylactic irradiation of intervention tracks (PIT), mostly thoracoscopic procedures. Most patients (84%) received either 21 Gy in three fractions or 20 Gy in four to five fractions. In the PIT group, 13% of the 48 patients developed biopsy tract metastases, compared with 33% of the 123 patients who were not radiated (P = .008). This difference was not statistically significant on multivariate analysis when analyzed as local progression-free survival at the intervention site at 6 or 12 months. The two systematic reviews included three RCTs.9,11,14 Both concluded that there was neither consensus nor strong justification for PIT, since only one RCT detected a significant difference in intervention site metastases after PIT. In this widely cited 40-patient trial, 21 Gy in three consecutive fractions delivered 10 to 15 days after thoracoscopy reduced intervention site metastases from 40% to 0%.14 An RCTon 58 sites in 43 patients with a much lower dose, 10 Gy in one fraction using 9-MeV electron therapy, reported no significant difference in tract metastases (10% v 7%). A 61-patient RCT compared 21 Gy in three fractions within 21 days after an invasive procedure with BSC. No statistical difference in tract metastases was detected.9 It is important to recognize that most published studies were performed prior to the widespread use of effective chemotherapy. Patients were also not treated with more comprehensive adjuvant radiation therapy techniques delivered to larger parts of the thorax. Interestingly, despite these data, 75% of United Kingdom survey responders routinely used PIT, and 80% were supportive of a larger RCT to determine its efficacy.204,216 This led to the largest, most rigorously performed multicenter, phase III RCT in 203 patients treated with immediate radiation therapy to 21 Gy in three fractions within 42 days of pleural intervention or deferred radiation therapy at the time of procedure-tract metastases.21 The primary end point was the incidence of tract metastases within 7 cm of the intervention site. No significant difference in tract metastases was identified (9% v 16%; P = .14). There was a suggestion that epithelioid-only histologic subtypes may benefit from PIT, and patients not treated with chemotherapy may have a lower tract recurrence rate with immediate radiation therapy. Further studies in these specific subgroups may be warranted.

What is the role of palliative radiation therapy? What is the optimal radiation dose and fractionation?

- Recommendation 2.1: Radiation therapy should be offered as an effective treatment modality to palliate patients with symptomatic disease (Type of recommendation: evidence based; Evidence quality: intermediate; Strength of recommendation: strong).

Literature review and clinical interpretation.

Until recently, the evidence for palliative radiation therapy in MPM was quite limited. A systematic review199 found that the literature consisted mostly of retrospective series and two small single-arm phase II studies that investigated palliative hemithoracic radiation therapy with antiquated techniques. A 111-patient retrospective series from 1994 demonstrated relief of symptoms, principally pain, in over half the patients, with no observed dose-response relationship. The largest retrospective study was in 189 patients treated for a total of 227 courses of radiation therapy.48 Pain, mostly from tumor growing into the chest wall, was the indication for palliative radiation therapy in 77%. While patients were treated with a various radiation therapy regimens, since 1987, sites of symptomatic disease in 91 patients were irradiated to a total dose of 36 Gy in nine fractions, three times weekly. There was a better response rate with radiation therapy doses of 4 Gy or higher per fraction (50% v 39%), with a median time to pain recurrence of 69 days. The highest-quality data are from the

Symptom Study of Radiotherapy in Mesothelioma (SYSTEMS-1), a multicentre single-arm phase II study of 40 patients treated to a total dose of 20 Gy in five fractions.[191] All treatments were planned based on CT and PET/CT imaging. Pain was characterized prospectively; 54% of patients presented with neuropathic pain.[196] This regimen decreased pain in 47% of patients. No improvement in QoL or other symptoms was detected, possibly due to the short survival after treatment. This study is limited by its relatively small sample size, high attrition rate, poor survival, and variability of radiation field and technique. A follow-up study (SYSTEMS-2) will examine whether a dose-escalated, hypofractionated radiation therapy approach (36 Gy in six fractions) results in clinically significant improvement in pain at 5 weeks when compared with standard palliative radiation therapy (20 Gy in five fractions). Palliative radiation therapy using standard palliative doses and fractionation can provide significant pain relief in about 50% of patients and should be considered in all patients with MPM with localized disease causing pain or obstructive symptoms.

Baas P et al., 2015 [1].

ESMO

Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

k.A.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität unklar.

Recherche/Suchzeitraum:

- k.A.

LoE & GoR

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Sonstige methodische Hinweise

- kein Methodenreport; unklar ob formalisiertes Konsensusverfahren angewendet wurde
- Repräsentativität der Gremien unklar
- Industriefinanziert
- Auswahlprozess der Literatur unklar
- Keine system. Bewertung der Validität der Studien, sondern “quality of data based on trial design”

Empfehlungen

Empfehlung 1

Recommendation 4
The first- and second-line treatment of unresectable mesothelioma

- *Anti-folate/platinum doublet is the only approved standard of care [I, A].*
- *Maintenance therapy (switch or continuation) has not yet improved the OS and patients should be included in these studies [II, A].*
- *Patients in good condition should be recommended to join studies in second line [II, A].*

front-line therapy for mesothelioma

Front-line chemotherapy improves survival of patients with unresectable MPM. Combination doublet chemotherapy of cisplatin, with either pemetrexed or raltitrexed, has shown a longer survival compared with cisplatin alone in randomised phase III trials [20, 21]. Carboplatin is an acceptable alternative to cisplatin and may be better tolerated in the elderly population [22, 23]. Several phase II clinical trials are investigating the addition of novel agents to pemetrexed/cisplatin therapy. To date, no agent has demonstrated superior efficacy. Although the agent CBP501 (a G2 checkpoint abrogator) met its primary end point, it was not considered to improve upon the efficacy of standard chemotherapy.

Trials of anti-angiogenic agents such as bevacizumab or sunitinib [24, 25] have so far failed to demonstrate improvementover standard treatment.

maintenance therapy for mesothelioma

The use of continuation or switch maintenance therapy with pemetrexed monotherapy has changed practice in the management of non-small-cell lung cancer, but is yet to be evaluated in the mesothelioma setting. However, a phase II trial addressing this question [NCT01085630], led by the Cancer and Leukemia Group B (CALGB), is currently underway. Switch maintenance, with the focal adhesion kinase inhibitor defactinib (VS6063) versus placebo, is currently under evaluation in the COMMAND trial [NCT01870609]. Another phase III, switch maintenance, study of gemcitabine versus observation is currently on-going in the Netherlands (NVALT 19). A recent phase III study evaluating switch maintenance to thalidomide was negative [26].

second-line therapy for mesothelioma

There is currently no second-line standard of care. Phase III evaluation of pemetrexed monotherapy in previously treated patients was not associated with longer survival when compared with best supportive care (BSC). Post-study chemotherapy has been shown to be associated with significantly longer survival, with an adjusted hazard ratio of 0.56 [27]. Single agent vinorelbine has shown useful activity in phase II trials [28, 29], demonstrating a trend towards longer survival as was seen in the firstline study (MSO1) [30].

There are promising developments in the novel agent arena, for example, anti-mesothelin immunotoxin [31]. Immunotherapy targeting CTLA4 with tremelimumab [32] is under evaluation in a large global phase III trial [NCT01843374]. Recent data suggest that the PDL1, a putative biomarker for PD1/PDL1 therapy, is significantly expressed in mesotheliomas, particularly the sarcomatoid subtype. In the absence of standard second-line or furtherline therapy, it is recommended that patients are enrolled into clinical trials.

Empfehlung 2

Recommendation 5

RT can be considered in the following cases

- *For palliation of pain related to tumour growth, RT can be considered [II, A].*
- *The use of RT to prevent growth in drainage tracts is not proved to be useful [III, A].*
- *RT can be given in an adjuvant setting after surgery or chemo-surgery to reduce the local failure rate. However, no evidence is available for its use as a standard treatment [II, A].*
- *When postoperative RT is applied, strict constraints must be adhered to in order to avoid toxicity to neighbouring organs, and special, tissue sparing, techniques should be used [II, A].*

radiotherapy

Radiotherapy (RT) can be used for different indications in mesothelioma: as palliation, as preventive treatment and as part of a multimodality treatment. For patients suffering from pain (e.g., by chest wall invasion), RT, prescribing usually short course regimens, can be considered although the systematic review by Macleod et al. [37, 38] suggested that no high-quality evidence currently exists to support RT in treating pain in MPM.

In the case of palliation, the aim of RT is to relieve pain and it is recommended in cases of infiltration of the chest wall or permeation nodules by MPM. The treatment is usually given in short courses such as 1 × 10 or 3 × 8 Gy. There is much debate whether a scar after thoracoscopy and/ or drainage procedures should be irradiated prophylactically in order to reduce the likelihood of seeding metastases. It is probably best to recommend refraining from this procedure unless in the setting of a clinical trial [39], such as the United Kingdom 'PIT' study (ClinicalTrials.gov Identifier NCT01604005). One randomised trial compared immediate drain site RT (21 Gy in three fractions) to observation in 61 patients treated between 1998 and 2004 [40]. The authors concluded that prophylactic drain site RT in MPM did not reduce the incidence of tumour seeding, as indicated by previous studies conducted in the 1990s. Quality control of RT, the use of first-line therapy and patient selection can probably explain the discrepancy of these results. Puncture points or thoracoscopy scars should be identified and checked for early irradiation as soon as the diagnosis of MPM is confirmed (expert advice). A randomised study of post-intervention radiation of the tract is accruing in the UK (PIT trial).

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 7 of 12, March 2019) am 15.07.2019

#	Suchfrage
1	[mh Mesothelioma]
2	mesotheliom*:ti,ab,kw
3	(#1 OR #2) AND pleura*:ti,ab,kw
4	[mh “Pleural Neoplasms”]
5	pleura*:ti,ab,kw AND (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions*):ti,ab,kw
6	{OR #3-#5}
7	#6 with Cochrane Library publication date from Jul 2014 to present

Systematic Reviews in Medline (PubMed) am 16.07.2019

#	Suchfrage
1	"mesothelioma"[mh] AND pleura*[tiab]
2	mesotheliom*[tiab] AND pleura*[tiab]
3	"pleural neoplasms"[mh]
4	pleura*[tiab] AND ((((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab])
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND

	(search*[tiab] OR research*[tiab])))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2014/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 15.07.2019

#	**Suchfrage**
1	"mesothelioma"[mh] AND pleura*[tiab]
2	mesotheliom*[tiab] AND pleura*[tiab]
3	"pleural neoplasms"[mh]
4	"pleura*[tiab] AND (((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) OR malignan*[tiab]
5	#1 OR #2 OR #3 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2014/07/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

Referenzen

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