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Articles selected and commented on by:

Shigehiro Yagishita, M.D., Kazuhisa Takahashi, M.D.Ph.D.

Department of Respiratory Medicine, Juntendo University, Graduate School of Medicine, Tokyo, Japan



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Molecular classification of malignant pleural mesothelioma: identification of a poor prognosis subgroup linked to the epithelial-to-mesenchymal transition.

Clin Cancer Res. 2014 Mar 1;20(5):1323-34.

<http://clincancerres.aacrjournals.org/content/20/5/1323.long>

Malignant pleural mesothelioma (MPM) has been histologically classified by using consensus guidelines of International Mesothelioma Interest Group (epithelioid, biphasic, sarcomatoid, and desmoplastic etc). Moreover, several genetic alterations have been reported in MPM patients with some effect of survival differences. However, it is still difficult to discriminate the biological differences and patient group who receive survival benefit by therapy. In this article, the authors conducted a transcriptomic classification of MPM and demonstrated two distinct subgroups (C1 and C2) by using transcriptomic microarray on 38 primary cultured cells. All sarcomatoid and desmoplastic MPM were included in C2 group with a worse survival compared to C1 group. This subgroup classification was validated in independent samples using three gene predictor (BAP1, CDKN2A, and CDKN2B). Moreover, the authors conducted pathway analysis and demonstrated that C2 group was characterized by a mesenchymal phenotype. In conclusion, the authors established a novel molecular classification which allow us to discriminate poor prognosis subgroups even in epithelioid subtype in MPM. Identification of molecular mechanism which encompass poor prognosis and therapeutic strategy for the molecular mechanism are urgently needed.

Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study.

Ann Thorac Surg. 2014 Jun;97(6):1859-65.

<http://www.sciencedirect.com/science/article/pii/S0003497514003300>

Extrapleural pneumonectomy (EPP) is one of the treatment choice for the malignant pleural mesothelioma (MPM) in which an en bloc resection of the lung, parietal pleura, pericardium, and diaphragm. Despite its difficulty and high perioperative mortality, the clinical relevance of EPP for the treatment strategy of MPM is not yet strictly established. In this article, the authors conducted retrospective analysis for assessing perioperative outcome and long-term survival after EPP by using collected data from nine referral centers for thoracic surgery in Italy. A total of 518 MPM patients including 84.4% with epithelial histology and 68% with pathologic stage three diseases were included in this analysis. Of these, 271 (52.3%) patients received induction chemotherapy and 373 (72%) patients received adjuvant therapy including 213 (41.1%) radiotherapy, 43 (8.3%) adjuvant chemotherapy, and 117 (22.6%) both radiotherapy and chemotherapy. Median overall survival was 18 months. Multivariate analyses showed female sex, epithelial histology, and trimodality treatment using induction chemotherapy were significantly associated with better survival. These results indicate that patient selection and proper neoadjuvant or adjuvant treatment would be a key for the success of EPP for MPM treatment.

A feasibility study evaluating Surgery for Mesothelioma After Radiation Therapy: the SMART" approach for resectable malignant pleural mesothelioma."

J Thorac Oncol. 2014 Mar;9(3):397-402.

<http://journals.lww.com/jto/pages/articleviewer.aspx?year=2014&issue=03000&article=00018&type=abstract>

The role of multimodality therapy for malignant pleural mesothelioma (MPM) has been open to debate. In this study, the authors conducted phase I/II study to assess the feasibility of Surgery for Mesothelioma After Radiation Therapy (SMART). A total of 25 patients who had resectable clinical T1-3N0M0 histologically proven MPM were included in this study. All patients received neoadjuvant hemithoracic intensity-modulated radiation therapy (IMRT) followed by extrapleural pneumonectomy (EPP). Thirteen patients experienced grade 3+ surgical complications and one patient died from treatment related empyema. Five of 13 ypN2 patients received adjuvant chemotherapy in accordance with study protocol. Median survival time was not reached after a median follow up of 23 months. Patients with epithelial histology (64%, 16/25 patients) had a better survival compared to biphasic histology (3-year survival rate: 84% vs 13%). In this study, the authors firstly demonstrated the feasibility of IMRT followed by EPP. Notably, all patients received EPP within 6 days after completion of IMRT which enabled to avoid pulmonary toxicity of IMRT. Moreover, survival analysis was appreciable considering the fact that the final pathological stage was relatively advanced (pathological stage IB/III/IV: 1/11/13). Further investigation in a larger study cohort is needed.

Anetumab Ravnansine: A Novel Mesothelin-Targeting Antibody-Drug Conjugate Cures Tumors with Heterogeneous Target Expression Favored by Bystander Effect.

Mol Cancer Ther. 2014 Jun;13(6):1537-48.

<http://mct.aacrjournals.org/content/13/6/1537.long>

Mesothelin is a glycosylphosphatidylinositol (GPI)-anchored glycoprotein which is highly overexpressed in several types of cancer including malignant pleural mesothelioma (MPM). Anticancer treatment targeting mesothelin has been developed and some of them are in clinical trials. In this article, the authors describe preclinical activity of novel antibody-drug conjugate (ADC), anetumab ravnansine (BAY 94-9343), which is a IgG1 type fully human anti-mesothelin antibody coupled with microtubule-targeting toxophore DM4. Recently, trastuzumab-DM1 (TDM-1), anti-HER2 antibody ADC, was approved for HER2-positive breast cancer and much attention have been payed for ADC treatment. The authors first assessed antitumor activity of BAY 94-9343 in vitro and clearly showed the high affinity and selective activity for mesothelin overexpressing cells in dose-dependent manner. Then, they conducted in vivo assay using patient-derived xenograft model. Notably, BAY 94-9343 showed tumor regression even when only 20% of mesothelin-positive cells within the tumor, indicating bystander effect of conjugated DM-4 toxophore. These data suggest the possibility of BAY 94-9343 for the treatment of MPM and the potency of targeting mesothelin. BAY 94-9343 is on a Phase I trial for advanced solid tumor and precise data of activity in cancer patients are needed.

B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis.

J Thorac Oncol. 2014 Jul;9(7):1036-40.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058651/>

B7 homolog 1 (B7-H1; aka programmed cell death 1 ligand 1) is a negative co-stimulatory molecule and is well known as a ligand of programmed death-1 (PD-1). B7-H1 has been reported to be a negative prognostic marker in several types of cancer, however, its positivity rate and prognostic effect in MPM are unknown. In this article, the authors conducted immunohistochemical analysis in 106 MPM patients cohort by using a mouse monoclonal anti-human B7-H1 antibody (5H1-A3 clone). B7-H1 positivity rate was 40% (42/106) and patients with B7-H1 positive tumor had more sarcomatoid histology (38% vs 2%, $p < 0.0001$) and poor prognosis (median survival: 5 vs 14.5 months, $p < 0.0001$) compared to patients without B7-H1. Among sarcomatoid histology, 94% (16/17 patients) had positive B7-H1 expression. There are several problems in the importance of B7-H1 immunohistochemistry as a biomarker for anti-PD-1 or anti-PD-L1 antibody, these results offer baseline data of B7-H1 expression in MPM.

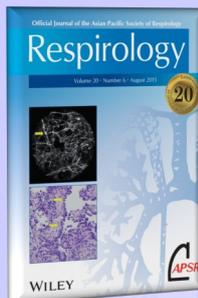
Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma.

Cancer Res. 2015 Jan 15;75(2):264-9.

<http://cancerres.aacrjournals.org/content/75/2/264.long>

Malignant pleural mesothelioma (MPM) is a rare and highly aggressive tumor which is associated with exposure to asbestos. Due to its rarity, there are still small number of report describing whole exome sequencing of MPM samples. In this study, the authors conducted whole exome sequencing by using 22 MPM tumor samples and matched blood samples. They found 517 somatic mutations in 490 mutated genes including tumor suppressing gene BRCA1 associated protein (BAP1), neurofibromin2 (NF2), cyclin-dependent kinase inhibitor 2A (CDKN2A), and cullin1 (CUL1). Furthermore, they found frequent genetic alterations in the cell cycle, MAPK pathway, and Wnt pathway. Notably, CUL1 was first to identified as somatic mutated gene in MPM. Despite the limited number of samples analyzed, these findings will provide us further insight for the mechanisms of oncogenesis in MPM.

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Germline Mutations in BAP1 Impair Its Function in DNA Double-Strand Break Repair

Cancer Res. 2014 Aug 15;74(16):4282-94.

<http://cancerres.aacrjournals.org/content/74/16/4282.long>

BRCA1-associated protein (BAP1) is a tumor suppressor gene which frequently mutated in several types of cancer including malignant pleural mesothelioma (MPM). BAP1 was originally isolated as a nuclear deubiquitylating enzymes (DUB) that interacts and enhances the growth suppressive effect of BRCA1. However, the precise mechanisms of BAP1 function as part of the DNA damage response. In this article, the authors clearly demonstrated that BAP1 is phosphorylated by ATM in response to DNA damage, and recruits to DNA damage sites together with AS-CL1 in a poly(ADP-ribose)-dependent manner. Furthermore, they showed germline BAP1 mutations inhibit DNA double-strand breaks repair and increase radiation sensitivity. They concluded that their results offer a new insights into the importance of ubiquitin turnover at sites of DNA damage and tumor suppressive function of BAP1. Further investigation for the mechanisms of BAP1 function and interaction with BRCA1 will provide us new treatment strategy for MPM.

Merlin deficiency predicts FAK inhibitor sensitivity: a synthetic lethal relationship

Sci Transl Med. 2014 May 21;6(237):237

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4165339/>

The authors found that the cells most sensitive to focal adhesion kinase (FAK) inhibition lack expression of the neurofibromatosis type 2 (NF2) tumor suppressor gene product, Merlin in a variety of cancer cell lines. Merlin expression is often lost in malignant pleural mesothelioma (MPM), an asbestos-induced aggressive cancer with limited treatment options. These data demonstrate that low Merlin expression may predict for increased sensitivity of MPM cells to a FAK inhibitor, VS-4718, in vitro and in tumor xenograft models. Weak cell-cell adhesions in Merlin-negative MPM cells contribute to their greater dependence on cell-ECM-induced FAK signaling. This finding may explain why Merlin-negative cells are vulnerable to FAK inhibitor treatment. Although pemetrexed and cisplatin enrich for CSCs, FAK inhibitor treatment preferentially eliminates these cells. The FAK inhibitor thus could potentially induce a more durable clinical response through reduction of CSCs along with a strong anti-tumor effect. Together, the data presented here provide strong rationale for a clinical trial of a FAK inhibitor administered to MPM patients with Merlin-negative tumors after first-line therapy with stratification based on Merlin protein expression.

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WILEY

Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients.

J Thorac Oncol. 2014 Mar;**9**(3):390-6.

<http://journals.lww.com/jto/pages/articleviewer.aspx?year=2014&issue=03000&article=00017&type=abstract>

Pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP) are sometimes chosen for selected patients with resectable malignant pleural mesothelioma (MPM). The aim of this study was to investigate the impact of surgical treatment on the outcome of patients with MPM. Data from 1365 consecutive patients with MPM, treated from 1982 to 2012 in six Institutions, were retrospectively reviewed. Patients who received chemotherapy alone (n = 172), best supportive care (n = 690), or surgical treatment (n = 503), by either P/D (n = 202) or EPP (n = 301) with or without chemotherapy, were enrolled in this study. Median survival for patients who received palliative treatment or chemotherapy alone, P/D, and EPP were 11.7 (95% CI, 10.5-12.5), 20.5 (95% CI, 18.2-23.1), and 18.8 (95% CI, 17.2-20.9) months, respectively. The 30-day mortality was 2.6% after P/D and 4.1% after EPP (p = 0.401). According to multivariate analysis (n = 1227), age less than 70, epithelial histology, and chemotherapy were independent favorable prognostic factors. In the subset of 313 patients (25.5%) with all favorable prognostic factors, median survival was 18.6 months after medical therapy alone, 24.6 months after P/D, and 20.9 months after EPP (p = 0.596). The modest benefit observed after surgery during medical treatment requires further investigation. Large multicenter, randomized trial, testing P/D after induction chemotherapy versus chemotherapy alone in MPM patients with good prognostic factors, is needed.

Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial.

Lancet. 2014 Sep **20**;384(9948):1118-27

<http://www.sciencedirect.com/science/article/pii/S0140673614604189>

Previous non-randomised studies suggested that video-assisted thoracoscopic partial pleurectomy (VAT-PP) might improve symptom control and survival in patients with malignant pleural mesothelioma. Authors therefore aimed to compare efficacy in terms of overall survival, and cost, of VAT-PP and talc pleurodesis. They undertook an open-label, parallel-group, randomised, controlled trial in patients with any subtype of confirmed or suspected mesothelioma with pleural effusion. Eligible patients were randomly assigned to either VAT-PP or talc pleurodesis. The primary outcome was overall survival at 1 year, analysed by intention to treat. 196 patients, of whom 175 (88 assigned to talc pleurodesis, 87 assigned to VAT-PP) had confirmed mesothelioma, were randomly assigned. Overall survival at 1 year was 52% in the VAT-PP group and 57% in the talc pleurodesis group. Surgical complications were significantly more common after VAT-PP than after talc pleurodesis. Median hospital stay was longer at 7 days in patients who received VAT-PP compared with 3 days for those who received talc pleurodesis

($p < 0.0001$). VAT-PP is not recommended to improve overall survival in patients with pleural effusion due to malignant pleural mesothelioma, and therefore talc pleurodesis might be preferable considering the fewer complications and shorter hospital stay.

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Articles selected and commented on by: Shigehiro Yagishita, M.D., Kazuhisa Takahashi, M.D.Ph.D. Department of Respiratory Medicine, Juntendo University, Graduate School of Medicine, Tokyo, Japan

Editor: Dr David CL Lam, Department of Medicine, University of Hong Kong, Hong Kong, China

Compiled by: Dr Christel Norman, Respirology Editorial Office, Perth, Australia

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