Editorial

Extra-pleural pneumonectomy in the setting of tri-modality therapy for patients with malignant pleural mesothelioma

Alexander Chi[1], Sijin Wen[2], Nam P. Nguyen[3], Geraldine Jacobson[1], Scot Remick[4], William Tse[5], Zhongxing Liao[6]

[1]Department of Radiation Oncology, West Virginia University, Morgantown, WV 26506, USA; [2]Department of Biostatistics, West Virginia University, Morgantown, WV 26506, USA; [3]Department of Radiation Oncology, University of Arizona, Tucson, AZ 85724, USA; [4]Mary Babb Randolph Cancer Center, Morgantown, WV 26506, USA; [5]Department of Hematology Oncology, West Virginia University, Morgantown, WV 26506, USA; [6]Department of Radiation Oncology, the University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Corresponding to: Alexander Chi, M.D. Department of Radiation Oncology, West Virginia University 1 Medical Center Dr. Morgantown, WV 26505, USA. Email: achiaz2010@gmail.com.

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Although declining in the US due to restrictions of asbestos exposure, malignant pleural mesothelioma (MPP) remains a very serious thoracic malignancy that is rising in incidence worldwide (1). Trimodality therapy with chemotherapy and radiotherapy combined with extrapleural pneumonectomy (EPP) has gained acceptance given the acceptable mortality rate (<5%) and long term survival reported in patients with epithelial histology, negative margins, and no extrapleural lymph node involvement after trimodality treatment (2). Since then, multiple studies have been published reported excellent median survival of >20 months after trimodality therapy (1). However, this treatment approach continues to be controversial given recent publications demonstrating that EPP may lead to poorer survival and increased mortality from surgery when compared with pleurectomy/decortication (P/D) (3-5). As shown in a large retrospective review of patients who have undergone EPP or P/D, the operative mortality was found to be 7% after EPP and 4% after P/D with a hazard rate of 1.4 for EPP found after multivariate analysis (P<0.001) (3). In a non-randomized prospective study comparing EPP and P/D in the setting of trimodality therapy, prolonged median survival was observed after P/D, hyperthermic pleural lavage with povidone-iodine, and adjuvant chemotherapy and prophylactic radiotherapy when compared with neoadjuvant chemotherapy, EPP, and adjuvant radiotherapy (23 *vs.* 12.8 months, P=0.004). Although improved survival is suggested, no conclusion regarding to whether EPP will lead to inferior survival when compared with P/D can be made due to the nature of these studies. In 2011, a prospective study (MARS) that attempts to compare EPP and P/D in a randomized fashion was reported (5). The aim of this study was to investigate the effect of EPP in the context of trimodality therapy *vs.* no EPP on the survival and quality of life in patients with malignant pleural mesothelioma. Due to the rarity of this disease, the feasibility of randomizing 50 patients in 1 year after neoadjuvant chemotherapy was explored. Among 112 patients registered between 2005 and 2008, 50 patients (T1-T3, N0-N1, and M0) were randomized to EPP *vs.* no EPP (24 *vs.* 26). Among the 24 patients randomized to EPP, the procedure was only completed in 16 patients (3 total operative mortalities) and 8 of these 16 patients received radical radiotherapy afterwards. While no significant differences between groups were reported in the quality of life analyses, the hazard ratio for overall survival between the EPP and no EPP groups were 2.75 (P=0.016) after adjusting for sex, histological subtype, stage, and age at randomization. Although the data analysis was appropriate, the sample size is too small to make any conclusion regarding to patient survival after EPP *vs.* no EPP (power calculation was based on 670 patients). Also, the final conclusion of EPP shortens survival is not supported by statistical inference, but just based on the descriptive statistics. For example, a formal boundary (a cutoff of a statistic) in the interim analysis should be used to make a statistical inference or conclusion. Therefore, the

conclusion of this study really needs to be interpreted with caution.

More recently, a systematic review of trimodality therapy for malignant pleural mesothelioma has been conducted (6). Among the 16 studies included, the median survival ranged from 12.8 to 46.9 months and the perioperative mortality varied from 0 to 12.5% but mostly <5%. Large variation in median survival has been observed, but 6 studies reported median survival of ≥20 months. Given the current level of evidence, further studies need to be conducted to further investigate the effect of EPP on the survival of patients with malignant pleural mesothelioma, especially when advanced technology is applied in the delivery of adjuvant RT, which may potentially improve the survival of patients with malignant pleural mesothelioma in the setting of both EPP and P/D (7,8).

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