A Feasibility Study Evaluating *S*urgery for *M*esothelioma *A*fter *R*adiation *T*herapy "*SMART*" Approach for Resectable Malignant Pleural Mesothelioma

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Neoadjuvant hemothoracic intensity modified radiation therapy (IMRT) followed by Extrapleural Pneumonectomy appears to be safe and potentially effective in patients with malignant pleural mesothelioma.

Background: With a disease incidence of approximately 3000-4000 cases annually in the United States (US), malignant pleural mesothelioma (MPM) is considered a rare but almost universally fatal malignancy.[2] Chemotherapy using pemetrexed combined with cisplatin or carboplatin represents the current standard of care.[3] However compared to best supportive care chemotherapy increases median survival only by 3 months. Median survival is 4 to 12 months without treatment and the 2-year overall survival is 0% to 12 %.[2] Based on the results of the recently reported MARS study, demonstrating increased mortality and diminished quality of life for patients treated with chemotherapy followed by extrapleural pneumonectomy (EPP) compared to chemotherapy alone[4] the therapeutic role for surgical disease reduction, EPP or radical pleurectomy/decortication remains highly controversial.[5]

Central Hypothesis: Neoadjuvant radiation therapy will decrease distant recurrences by preventing tumor cell dissemination during surgical resection

Design and Goal: Single Center Phase I/II study investigating the feasibility, safety and therapeutic effect of the neoadjuvant administration of a short accelerated course of high-dose hypofractionated hemithoracic radiation followed by EPP in patients with MPM.

Patients: MPM patients with clinical stage T1-3, N0, M0 (based on clinical evaluation, chest CT, PET-CT and brain MRI/CT), good performance status (ECOG 0-2) and good pulmonary function (FEV1 and DLCO > 40%) considered to be surgical candidates for EPP.

New Treatment Approach: Patients received neoadjuvant radiation to the ipsilateral hemithorax (clinical target volume: thoracic inlet to the diaphragmatic insertion, including biopsy and drainage tract sites) The dose prescription to the clinical target volume was 25 Gray in five daily fractions over approximately 1 week with a concomitant boost of 5 Gy to the gross tumor volume and tract sites using multibeam intensity modified radiation therapy (IMRT) technique. This represents a lethal dose to the lung. Approximately 1 week after completing IMRT all patients underwent standard EPP.

Outcomes: 25 patients (18%) of all screened patients were enrolled between 2008-2012. The most common reasons for exclusion included advanced disease, co-morbidities and patient refusal. All 25 patients completed IMRT and EPP. IMRT was well tolerated. EPP was performed 6 ± 2 days after completion of IMRT. Thirteen patients (52%) developed Grade 3+ surgical complications with the main complication being atrial fibrillation (n=5). There was no death within 30 days of surgery or during the postoperative hospital stay. One patient (4%) died 88 days after treatment due to empyema. Consistent with previously published data most patients were upstaged at the time of EPP. (Stages III n = 11 or IV n = 13) All patients with N2 involvement received adjuvant chemotherapy. The median follow-up was 23 months (range, 6–51 months). In contrast to biphasic cases, patients with epitheloid histology had a very favorable three-year progression free (65%) and overall survival (84%). (Figure 3 [1]) There were 11 recurrences 9 involved distant metastasis.

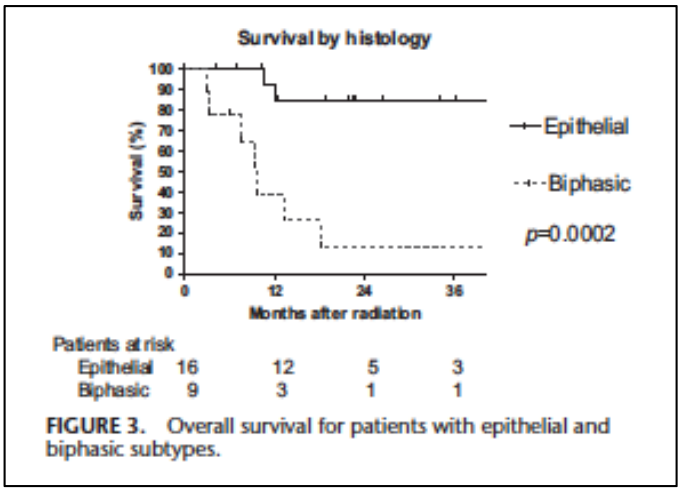

FIGURE 3. Overall survival for patients with epithelial and biphasic subtypes.

Main Results: High dose ipsilateral IMRT is feasible and safe prior to EPP. In patients with epitheloid histology this approach resulted in an excellent 3-year progression free and overall survival. However the hypothesis that this strategy would preferentially eliminate distant recurrences could not be established.

Conclusion: This small single center Phase I/II study suggests that neoadjuvant IMRT (SMART) has the potential to remarkably improve progression free and overall survival in patients with epitheloid MPM, clinical stage T1-3, N0, M0 (Stages I – III) who are surgical candidates for EPP.

Comments: The results presented in this small Phase I/II study are very intriguing and thought provoking. SMART therapy may represent a potential breakthrough for the management of patients with MPM who are candidates for EPP. Following the recently published results of the MARS study, the role of EPP as part of a multimodality approach in MPM patients has been questioned and remains highly controversial.[4,5] Recently, lung sparing surgical techniques such as pleurectomy/decortication (P/D) followed by adjuvant IMRT have been shown to be potentially superior to EPP, and extended P/D will be compared to chemotherapy alone in the MARS II study.[6-8,9] This lung preserving approach represents an alternative for patients who may otherwise be candidates for the SMART. Whereas improved lung function and lower procedural morbidity and mortality may favor P/D, the outcomes presented here are unprecedented in MPM. SMART may represent the preferred for patients with a significant disease burden in the pulmonary fissures which is difficult to remove during P/D.

The current study has several limitations. It includes a small number of highly selected cases (17 epitheloid MPM cases) with limited follow up. Given the administration of a “lethal” dose of radiation to the ipsilateral lung, the success of SMART therapy depends on close coordination between radiation therapists and thoracic surgeons. EPP needs to be feasible and patients need to be able to tolerate the procedure within a week of completing IMRT. Treatment related toxicities were rare and expected complications such as radiation pneumonitis of the contralateral lung were not observed. It is possible that the predominance of right-sided cases, 21/25 cases, facilitated safe IMRT however details of IMRT are yet unknown and will be reported separately. One is also left to wonder if more aggressive pretreatment clinical staging using routine EBUS and/or EUS or mediastinoscopy would have identified additional cases with significant nodal involvement (=>N2) and resulted in even better outcomes.

Furthermore it remains questionable if the observed benefits of SMART are indeed due to a lower risk for tumor cell dissemination at the time of surgery. The almost universal presence of distant disease at the time of recurrence would argue against that. It is certainly possible that immune stimulation by neoadjuvant IMRT may represent a potential mechanism of the therapeutic benefit of SMART.

In summary SMART represents a very exciting new treatment strategy for epitheloid MPM. This strategy may be most applicable to patients who are not candidates for lung sparing surgery due to extensive fissural involvement. Larger studies are clearly needed. Based on the MARS experience a randomized Phase III trial will be challenging however it should be attempted. A possible approach would be to compare multimodality therapy including extended P/D with SMART. Furthermore correlative studies to investigate the mechanisms behind the therapeutic benefit of SMART, e.g. enumeration of circulating tumor cells and characterization of anti-tumor immunity are needed.

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