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Feasibility trial assessing intrapleural photodynamic therapy combined with pleurectomy/decortication then chemotherapy in malignant pleural mesothelioma patients.

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ABSTRACT

Background: Multimodal treatment associating surgery (pleurectomy/decortication, P/D) then IV adjuvant chemotherapy (platinum/pemetrexed) is an effective therapeutic option for some selected malignant pleural mesothelioma (MPM) patients. Intra-operative pleural photodynamic therapy (iPDT) has emerged as a promising option to improve this multimodal treatment outcome (Friedberg J, Ann Thorac Surg. 2017). The MesoPDT trial (NCT02662504) aimed at assessing the feasibility of such procedure outside the only two US expert centers performing multimodal treatment including iPDT to date.

Methods: A single-center pilot clinical trial was designed to assess the feasibility of iPDT protocol in Lille University Hospital. A pool of maximum six patients was expected in order to apply the iPDT protocol, and to assess its applicability and safety outside US center expert.

Results: In 2016-2017, four consecutive assessable patients were included and treated per protocol, reaching the study achievement cut-off. iPDT specific procedures have been applied and managed in partnership with US experts. The safety profile was favorable. The main and most specific adverse event was acute lung injury occurring within 72 hours after iPDT, which may lead to reversible respiratory distress, manageable with adequate intensive care. The 4 patients achieved the full scheduled protocol.

Conclusion: The iPDT multimodal treatment for MPM is applicable and manageable in a European expert center, involving local skills and dedicated teams. The safety profile of the iPDT in Lille center was favorable, as validated by an external board. Median overall survival was promising (\approx 28 months), similar to previous US results. Our center is expected to join soon a large phase II randomized, multicentric US trial assessing MPM multimodal treatment (P/D, chemotherapy) \pm iPDT (NCT02153229; UPENN, USA).

Keywords: malignant pleural mesothelioma, Photodynamic therapy, Clinical study, photofrin

1. INTRODUCTION

1.1 Malignant pleural mesothelioma (MPM)

Malignant pleural mesothelioma (MPM) is an aggressive serosal tumor of the pleura. Its main aetiological agent is an exposure to asbestos fibers, mostly work-related, and the disease appears after a latency of 30 to 40 years after initial exposure. Malignant mesothelioma can rarely occur on other serosal surface such as the peritoneum, the pericardium and the tunica vaginalis testis. MPM is considered as a rare tumor. However, its incidence is rising throughout the world because of the increasing use of asbestos until the 1970's and will peak in the next decade. A pandemic rise of MPM in the future with developing countries still using asbestos today is expected. MPM has a poor prognosis with a median survival of less than a year. This can be explained by the delay of diagnosis due to late symptoms, with a disease already advanced locally, the difficulty of obtaining a confident anatomopathological diagnosis, and a complex treatment with deceiving outcomes. The three main histologic subtypes of MPM are epithelial, which is the most common and associated with a better prognosis, biphasic and sarcomatoid.

Treating MPM remains a challenge and there are two main alternatives: palliative chemotherapy or multimodal treatment including surgery, combined with chemotherapy and/or radiotherapy [1]. MPM shows a strong resistance to chemotherapy, which is often the unique treatment available for patients with advanced and unresectable disease, or who cannot sustain a heavy thoracic surgery. Cisplatin and pemetrexed based chemotherapy remains the reference for the first line of chemotherapy [2] with a median survival of 12.1 months [3]. Surgery offers the best chance of survival for this still incurable disease. However, after the most complete tumor resection, microscopic tumor cells persist and surgery should be associated with a local adjuvant treatment. Classically, hemithoracic radiotherapy is performed after thoracic surgery, especially after pneumonectomy [2]. Up to this day, there are no international recommendations on surgical treatments with a curative intent. Surgery is still investigational and should be part of a multimodality treatment and included in a prospective clinical trial. Pre-operative staging of MPM is done with a TNM system proposed by the International Mesothelioma Interest Group (IMIG) 1995, using the chest CT scan and TEP scanner. There are two leading types of surgery in the treatment of MPM: extrapleural pneumonectomy (EPP) (figure 1) and pleurectomy/decortication (P/D) (figure 2), or radical pleurectomy. The goals of surgery are to obtain a complete macroscopic resection of the tumor and symptom control. EPP consists of an "en bloc" resection of the lung, visceral and parietal pleura, pericardium and diaphragm whereas P/D preserves the lung and is therefore less disabling. A modified EPP (MEPP) attempts to preserve the barriers of the peritoneum, pericardium, abdomen and phrenic nerve to the diaphragm. P/D is defined by the resection of the visceral and parietal pleura, and is referred to "extended P/D" when the pericardium and/or the diaphragm need to be resected [4]. Pleurectomy associated with a lobectomy (P/L) can be performed as well.

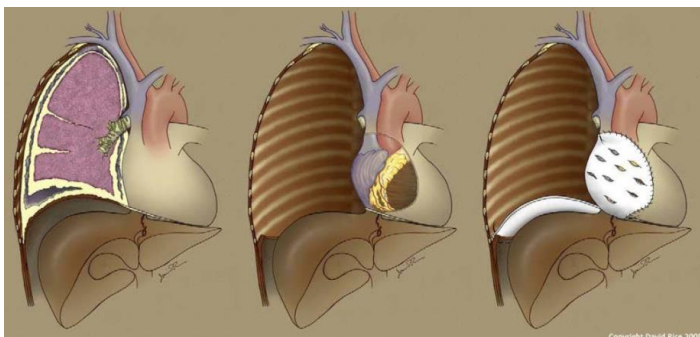


Figure 1: Extrapleural Pneumonectomy (EPP) [3]

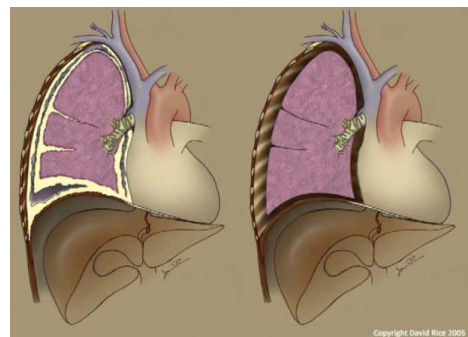


Figure 2: Pleurectomy Decortication (P/D) [3]

Even after optimal surgery and perioperative chemo-radiotherapy, local or distant recurrences are inevitable. In order to kill the residual microscopic disease after surgery and to obtain local control of the disease, many teams have worked on intrapleural therapies. With the objective of limiting the toxicity of systemic chemotherapy and enhancing local drug absorption, intrapleural hyperthermic chemotherapy was evaluated in phase I and phase II studies: cisplatin-based chemotherapy after P/D [5], or after EPP [6]. Another team performed a lung-sparing treatment including intrapleural chemotherapy combined with intrapleural P32 radiation. Intrapleural immunotherapy and gene therapy [7] were also performed but without prior surgery. These intrapleural therapies are deemed feasible, but are not conclusive enough due to insignificant survival gain, important side effects or the small size of the cohorts. In search of a more effective and selective adjuvant treatment to surgery, and in line with these intrapleural therapies, intra-operative photodynamic therapy (PDT) could be of interest in part of a multimodal treatment of MPM.

1.2. Photodynamic therapy

Photodynamic therapy is a treatment of ancient principle and became acknowledged as an innovative oncological treatment in the 1970's by Dougherty et al [8]. The effect of PDT requires the interaction of 3 components: a photosensitizer (PS), oxygen and light with the specific wavelength activating the PS. None of them are individually toxic but when put together they induce a tumoricidal photochemical reaction

There PS classically used in the treatment of MPM are porfimer sodium Photofrin® and m-tetrahydroxyphenylchlorin (m-THPC) Foscan®. The effect of PDT depends on the type and dose of PS used, the light dose and the oxygen concentration in the tissue illuminated. The appeal of PDT as an adjuvant treatment relies on its relative tumor selectivity, depending on a PS able to direct itself and remain longer in the tumor cells than in the normal cells, and an illumination restricted to the cancer superficial zone. Intrapleural PDT is based on a two-stage process: intravenous administration of a photosensitizer with a specified drug dose and drug-light interval (DLI) before surgery, and intraoperative illumination of the pleural cavity, after maximal resection of the tumor, by a laser source at an appropriate wavelength, and at a specified light dose.

MPM is essentially a localised disease, confined to the hemithorax. Since PDT is a local treatment, it seems legitimate to consider intrapleural PDT as a good candidate to eradicate the microscopic tumor cells remaining after any kind of surgical resection. For a few decades, photodynamic therapy has been the subject of many studies as part of a multimodal treatment of malignant pleural mesothelioma, including maximal tumor resection surgeries.

In 2012, Friedberg et al [9] published a very positive clinical study on 38 patients with MPM (stage III-IV 97%). Among these 38 patients, 28 were treatment naive and went directly to Radical Pleurectomy & PDT, with the intention of following with four cycles of pemetrexed-based chemotherapy. Ten patients were referred after chemotherapy, primarily for progression, and underwent Radical Pleurectomy -PDT with individualized adjuvant treatment recommendations. Each patient received intravenous porfimer sodium 2 mg/kg 24 hours preoperatively. Laser light, 630 nm, was delivered to a measured dose of 60 J/cm², as registered on seven strategically placed isotropic light detectors using a custom-built dosimetry system. The chest was filled with 0.01% dilute intralipid solution to facilitate light dispersion. Light delivery typically took approximately one hour to complete.

The results were very impressive with a survival of 31.7 months (95% confidence interval [CI], 9.0 –54.3 months) and a median progression-free survival for all patients of 9.6 months (95% CI, 6.8 –12.4 months)

The clinical study clearly demonstrated that radical pleurectomy is an operation that can be used to achieve macroscopic complete resection and, combined with intraoperative PDT, can be performed with very low mortality and acceptable morbidity. Besides, the authors concluded that this operation can be planned preoperatively, even in patients generally not thought to be candidates for lung sparing procedures, and does

not have to be reserved for patients who would not tolerate pneumonectomy. At last, they stated that PDT did not appear to have a positive impact on local control but may have played a role in extending survival for a duration well beyond that which would commonly be expected for recurrence after surgical resection in this cohort of patients. This particular combination of treatments yielded an unexpectedly long survival for patients with advanced-stage epithelial.

2. MATERIALS & METHODS

2.1 Intraoperative PDT

The MesoPDT trial (NCT02662504) aimed at assessing the feasibility of such procedure outside the only two US expert centers performing multimodal treatment including iPDT to date. The protocol is very similar to the one developed by Frideberg et al [9]. AS, PH and SM have had the opportunity to learn the technique while attending a surgical procedure in the Division of Thoracic Surgery in Philadelphia in March 2012.

Briefly, light precautions, fluid management, arterial lines and central venous lines, incision, airway management and surgical considerations for a patient undergoing a macroscopic complete resection and PDT for mesothelioma were similar to those already described by Friedberg et al [10]. Only 2 devices were slightly different: i) the light wand which was specifically designed by OncoThAI for this application. This light wand, made of a cylindrical diffuser located inside an endotracheal tube (figure 3), was fixed in a tank filled with dilute 0.01% intralipid and was carefully characterized before its use [11] (Figure 4). Similarly, OncoThAI developed a dosimetry system (mesoPDT dosimeter) similar to the system developed by the expert team of the University of Pennsylvania. This dosimetry system had the ability to process the information gathered by several detectors placed at strategic locations in the chest cavity and provided a real-time display, with the dose rate being detected at each light detector location and the cumulative dose (figures 5 & 6).



Figure 3: light wand developed by OncoThAI

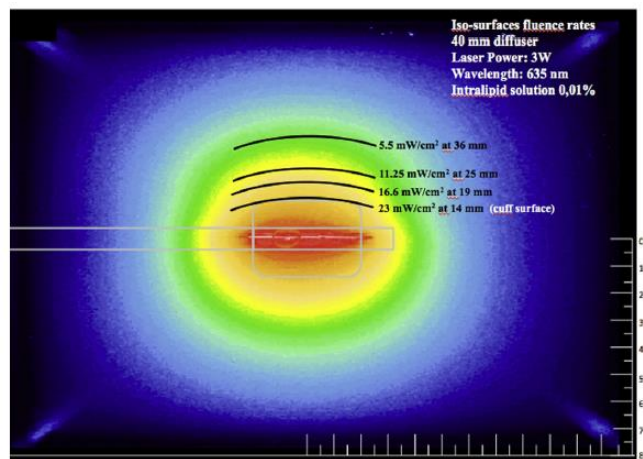


Figure 4: Illumination profile of the light wand for power output of 3 W. Fluence rate iso-surfaces localizations regarding the cuff of the applicator [11]

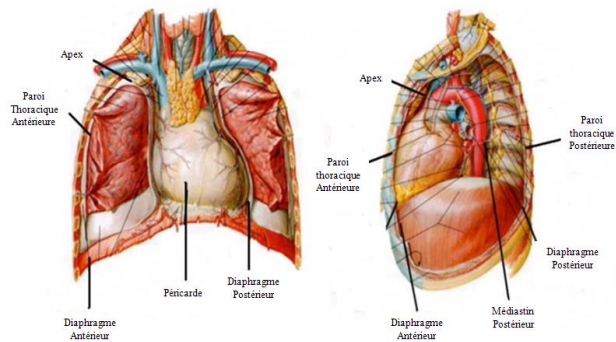


Figure 5: 7 isotropic light detectors are placed at strategic locations in the chest cavity: anterior sulcus, posterior sulcus, apex, anterior chest wall, posterior chest wall, pericardium, and posterior mediastinum.

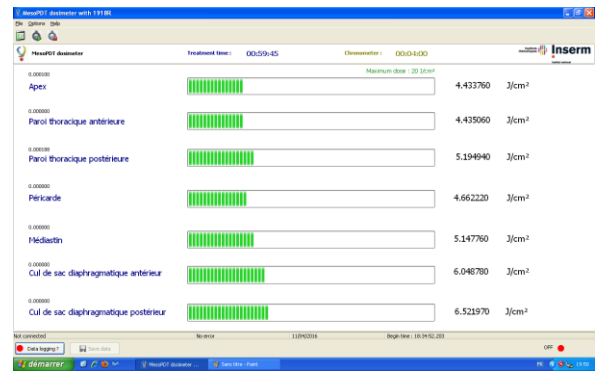


Figure 6: Screen shot of the MesoPDT dosimeter

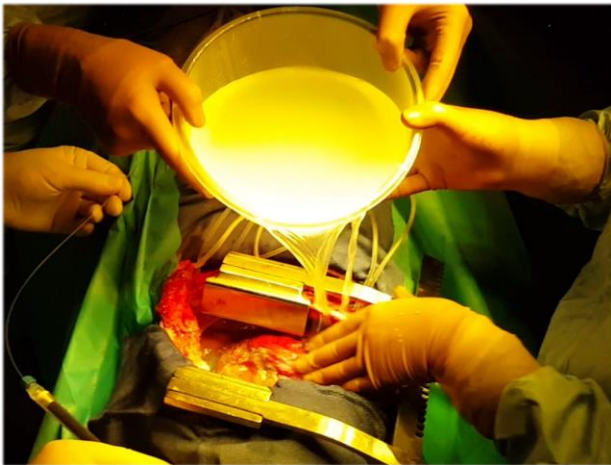


Figure 7: Before illumination, the chest is filled with 0.01% warmed intralipid solution.



Figure 8: illumination of the chest cavity during the procedure.

2.2. Postoperative Considerations

After the procedure, the patient must be taken to the ICU where postoperative care after the surgical procedure is of great importance.

3. RESULTS

4 patients were included from February 2016 to February 2017. Details on each patient is given in Table 1. Pleurectomy Decortication was followed by intraoperative PDT on 2 males and 2 females were included in this study.

Using the TNM classification (T category describes the primary tumor site, N category describes the regional lymph node involvement •M category describes the presence or otherwise of distant metastatic spread.), the 1st patient was pT3N1M0, the 2nd, pT3N2M0, the 3rd pT3N0M0 and the last one pT2N0M0.

The illumination duration varied from 46 minutes to 60 minutes. The lowest dose was 7 J/cm² and the highest dose was 15 J/cm²

Patient n°	Sex (H/F)	Age	Surgery Duration (hours)	Illumination duration (minutes)	Dose min/max (J/cm ²)	TNM	Status
1	F	53	13h50	56	10/15	pT3N1M0	III
2	H	71	12h30	60	10/14	pT3N2M0	III
3	F	62	12h30	52	7/11	pT3N0M0	III
4	H	67	12h30	46	10/12.5	pT2N0M0	II

Table 1: Patient Demographic, Treatment Variables and Staging

Postoperative complications, length of stay in this hospital are also reported (Table 2). All patient experienced important complications which required to stay in the hospital from 25 days up to 43 days.

Patient n°	Surgical Outcomes			Follow-Up
	Postoperative complications	ICU required	Length of Hospital stay (days)	
1	Acute Respiratory Distress Syndrome (ARDS) Pneumonia Dilatation of the right ventricle	yes	25	Data not available
2	Atrioventricular block (bradycardia), Low cardiac output, Broca's aphasia with right hemineglect Non-infectious intra-thoracic fluid collection	yes	43	Data not available
3	Acute Respiratory Distress Syndrome (ARDS) Tracheobronchitis - Bolster infection Pyrexia - Delayed healing of the thoracotomy scar	yes	40	Data not available
4	Sub-occlusive syndrome due to jejunostomy Pneumonia Bacteriemia (S. aureus) Subsegmental left pulmonary embolism Minimal pericardial effusion	yes	26	Data not available

Table 2: surgical outcomes

4. DISCUSSION & CONCLUSION

This paper is a preliminary report on a feasibility trial assessing intrapleural photodynamic therapy combined with pleurectomy/decortication then chemotherapy in malignant pleural mesothelioma patients. Consequently, it not possible to give conclusions. On May 30, 2019, the overall survival in the MesoPDT study is quite similar to the 31.7 months for all patients including those with the nonepithelial subtype reported by Friedberg et al [9]. The progression-free survival is higher in MesoPDT. However, the MesoPDT is limited to only 4 patients. Concerning the light parameters used in MesoPDT, it appears that the total dose used in our study is lower compared to those reported by Dimofte et al [12]. In MesoPDT, the average light dose deposited in the chest cavity was 11.2 J/cm² (7 to 15) compared to 60 J/cm². On 12 patients, Dimofte reported that the average duration of illumination was 65 minutes compared to 53.5 minutes in MesoPDT.

5. ACKNOWLEDGMENTS

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