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Results with radical resection in the management of malignant mesothelioma

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SUMMARY

Fifty-six patients treated by radical pleuropneumonectomy (RPP) for diffuse malignant mesothelioma (DMM) from 1987-1995 (8 years) had a mean age of 63.8 years. Pre operative diagnosis was definitely established in every case. The standard operation included radical resection of the lung with its pleural envelope, the hemidiaphragm and pericardium with reconstruction. GROUP I (1987-1990): 13 patients had no chemotherapy. GROUP II (1990-1995): 43 patients had 4 pulses of post operative chemotherapy at 4-weekly intervals. Operative mortality improved from 25% in the first 2 years to 15% in the last 2 years (16.2% for the whole Group II). Two-year actuarial survival was 7.6% for Group I, 23% for Group II (p=0.058). One patient survives for longer than 5 years without any evidence of recurrence. After the side effects of chemotherapy the quality of life was gratifying in most cases. In conclusion RPP can be considered as an important first step in the multi-modality treatment of DMM, with appropriate adjuvant treatment to control micrometastatic disease, so that survival can be improved.

INTRODUCTION

DMM has been known as an "incurable" disease, causing the patients' death within 8.4 months on average after diagnosis. Single-modality therapeutic attempts had disappointing results.

Progress can only occur as long as one tries to improve one's therapeutic effort by analysing the already accumulated data, which await to be accurately interpreted. For these reasons we retrospectively present our experience with treating DMM patients in our Unit, where the Treatment Protocol has changed during the last years.

There is already well-documented association of DMM with exposure to asbestos, with a variable latency period of as many as 35 years between the exposure and the clinical manifestations (Harvey JC et al, 1994).

DMM is not a disease of the past. Its Incidence in Scotland has been increasing, from 0.5 (per 100,000 population) in 1970 up to 4.9 in 1994.

MATERIAL AND METHODS

In our Unit 56 patients have been operated on during over the last 8 years (August 1987 - September 1995), after a definite histological diagnosis of DMM had been established by Open Pleural Biopsy in all cases. Other investigations necessarily included Respiratory Function Tests, CT and quantitative Ventilation / Perfusion scanning.

Thirteen out of these 56 patients had undergone radical surgical resection alone before 1990 and they comprised the GROUP I of our series.

The GROUP II consists of the 43 more recently treated patients, who have had the same resectional procedure followed by post operative Chemotherapy.

Both groups' patients were comparable in terms of mean age (65, 63.5 years) and predominant male-to-female ratio (12:1, 36:7 respectively).

Selection of cases is all important for this major operation with high risk. The tumour had to be confined on CT scanning to one hemithorax without extension into the chest wall. The patient should be assessed as fit for a major operation, in terms of medical history, age and respiratory function of the contralateral lung.

Patients of both groups underwent standard RPP as described by E.G. Butchart in 1976; the ipsilateral hemidiaphragm and pericardium were resected and reconstructed by prosthesis (Butchart 1976, Allen et al., 1994).

Post operative chemotherapy was systemically administered to the patients of the 2nd Group only. This consisted of 4 pulses of Carboplatin (1 g i.v.) and Epirubicin (40 mg/m^2 of body surface area), given 4-weekly.

RESULTS

MORTALITY.- The post operative 30-day and In-hospital mortality was as high as 25% in the earlier years 87-89 (Group I). Then it decreased down to 17.4% in 90-92 and even further down to 15% in 93-95, contributable to improved anaesthetic techniques, enhanced surgical experience and improvements in post operative Monitoring and Care. The post operative mortality for the whole Group II (43 patients) was therefore 16.2%.

MORBIDITY.- Post operative complications included arrhythmias requiring intravenous medication (26.8%), Sputum Retention or Chest Infection requiring mini-tracheostomy (26.8%) and Adult Respiratory Distress Syndrome (12.5%). Haemorrhage (5.3%) was a major problem in the early patients of this series, before the introduction of Trasylol intra operatively, which has since reduced blood loss considerably.

ACTUARIAL SURVIVAL.- The actuarial Survival was calculated according to the Kaplan-Meier method. (fig. 1). Patients of Group I, who only had RPP alone, had a 7.6% 2-year actuarial survival. They all died within $2\,^1/_2$ years post operatively. Patients in the 2nd Group, who had both, RPP and adjuvant chemotherapy, had a 2-year actuarial survival of 23% and 3-year of 14%. The longest survivor to-date is 5.7 years.

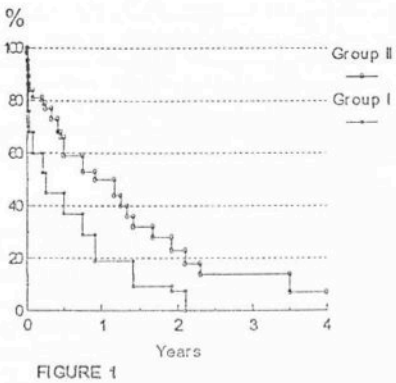

FIGURE 1

The number of the patients does not allow for statistically significant difference to be reached at this stage of reviewing our experience, as this is expressed with a p value of 0.058.

QUALITY OF LIFE.- The quality of the survivors' life was most gratifying. The Karnofsky Scale was used during their assessment at the out patients' Clinic and the Survivors' Status characterised as "Very Good" / "Fairly Good" / "Moderate" or "Poor" (Karnofsky scores 80-100, 50-79, 30-49 and 0-29 respectively). Patients doing VERY WELL (42.9%) were assessed as long as 20 months on average after their operation (and even up to 50 months in one case!). The patients who were FAIRLY WELL (19%), were also seen doing so a long time post operatively, namely 12.5 months on average (in some cases up to 24 months). On the other hand, patients doing POORLY (14.3%) were found at such a status as early as 2 months post operatively. This was due to either post operative complications or chemotherapy side effects or early recurrence of DMM.

RECURRENCES.- Twenty-three percent (23%) of the total patients had proven recurrent tumour. Most of the recurrences took place within the 1st year post operatively. Afterwards, the recurrence rate decreased. Most of the recurrences (53.8%) were located into the abdomen (hepatic, splenic, inferior vena caval, peritoneal sites etc.). Fewer recurrence locations were found in the chest or the thoracotomy wound. This occurred in 15.4%. Finally, sites of metastatic spread such as the brain, the contralateral lung or lymph nodes, were proven in 7% at each site.

DISCUSSION

In a comparison of Results after RPP so far reported, there has been considerable improvement in both, mortality and 2-year survival rates, after the pioneering work by E.G. Butchart in 1976.

Analysis of Ruffie's series (23 cases) gave a 2-year survival of 17% with operative mortality of 14% with pleuropneumonectomy alone (Ruffie et al 1989)

Most recent series have included some adjuvant therapy with benefit. In 1991 Sugarbaker reported 2-year survival of 48% with operative mortality of 6% in a series of 31 patients, treated by RPP followed by post operative cis-platinum-based chemotherapy with or without radiotherapy. However these results have not been matched elsewhere.

Allen's figures are the bench mark we strive to achieve (2-year survival 22.5%, operative mortality 7.5% in a 40-case series with post operative chemotherapy) (Allen KB et al, 1994).

There have been other surgical procedures proposed, such as pleurectomy with or without decortication with post operative chemotherapy (Branscheid D. et al. 1991, Allen KB 1994, Rice TW et al., 1994), aiming mainly for effective palliation. These

procedures are "cytoreductive", but they cannot achieve total removal of the tumour, which is undoubtedly desirable, at least on theoretical basis, if the aim of the treatment is with a curative intent. The only advocated benefit of these less extensive procedures is their more favourable mortality and morbidity.

However RPP in the context of multimodality treatment can nowadays be performed with acceptable mortality rates in selected patients.

The most common location of recurrence in our series was intra abdominal and this reflects the adequacy of local control of the disease within the chest with RPP.

New chemotherapeutic agents and intrapleural application are still to be further explored and expected to provide an improved outcome. A third group of patients is currently being treated in our Unit by RPP followed by Local Application of chemotherapeutic agents (above and below the reconstructed diaphragm) and systemic (i.v) chemotherapy.

Therapeutic nihilism has been popular, but advocating "No Specific Treatment" or "Supportive Care Alone" denies any future development of potentially curative Treatment regimens.

CONCLUSIONS

A radical resectional procedure can be considered as an important first step in the multi-modality treatment of DMM, with appropriate adjuvant treatment to control micrometastatic disease, so that survival can be improved.

Post operative Mortality and Morbidity are reduced with enhanced surgical and anaesthetic experience.

The quality of life of the long-surviving patients post operatively is very good, unless and until recurrence takes place.

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