

## Metastasectomy and hyperthermic isolated lung perfusion with TNF and melphalan in the treatment of multiple pulmonary metastases from sarcomas

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### Aim

Even in patients treated with complete resection of multiple lung metastases from sarcomas and systemic chemotherapy, pulmonary recurrence is frequent. This supports the need for a multimodality approach, in which surgery would remove all the detectable tumor burden, while regional chemotherapy would eradicate the microscopic foci. Sarcomas represent an ideal model for pulmonary perfusion, since metastases often remain restricted to the lung, at least during the initial distant spread phase. For the isolated lung perfusion, we adopted the same therapeutic schedule that had already proved to be effective in the regional treatment of limb sarcomas: hyperthermia, TNF and melphalan. The aim of the present study was to assess the feasibility and safety of the multimodality approach, as well as its pulmonary parenchyma toxicity.

### Methods

In a previous experience from our group using normothermic lung perfusion with platinum, a conspicuous interstitial and alveolar edema developed in the treated lung during the first 48 hours from treatment. Consequently, in the present study single lung perfusion was used. Six perfusions were performed in four

patients. Staged thoracotomies were used in two patients with bilateral metastases. The administered doses of TNF (1 mg) and melphalan (30 mg) were chosen according to the literature data. Half doses (0,5 mg of TNF and 15 mg of melphalan) were preliminarily tested in two patients without any toxic effect. Inclusion criteria were: 1) complete control of the primary sarcoma; 2) no extrapulmonary metastases; 3) multiple lung metastases judged to be completely resectable; 4) vital organ function consistent with the planned treatment; 5) signed informed consent. At surgery, all metastases were first identified and traced. Regional chemotherapy was given as the first treatment because blood supply was not compromised as yet. The pulmonary artery and a portion of the left atrium were occluded by vascular clamps and cannulated. The canulas were connected to the perfusion circuit, basically consisting of an oxygenator, a roller pump, a reservoir, and a heat exchanger. Hyperthermic lung perfusion was performed for 90 minutes. The circuit to systemic circulation leak was measured by 99m Tc (5 MBq) labeled eritocytes. Lung damage was assessed at 1, 3, 6 and 12 months from perfusion by blood gas analysis, spirometry, and CO<sub>2</sub> diffusing capacity; trans-bronchial biopsies were carried out in two patients at 1 and 3 months from treatment.

### Results

The mean circuit to systemic circulation leak was 6.5%/hr. Lung temperature range was 40.5-41.3 °C; lung perfusion flow rate was maintained between 370-510 ml/min, and mean pulmonary artery pressure did not exceed 50 mm Hg. Lung perfusion was accomplished without any lethal consequences, peri-operative complications or systemic toxicity. Patients were

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mechanically ventilated for 24 hours after surgery, and no interstitial or alveolar edemas developed. The decrease of FVC and FEV1 values were compatible with the amount of the removed lung parenchyma. Transbronchial biopsies evidenced mild interstitial fibrosis. In two patients who completed the 12 month follow-up, CT scan showed no pulmonary relapse.

## **Conclusions**

Hyperthermic lung perfusion with TNF and melphalan, coupled with metastasectomy, is feasible and safe. Systemic toxicity is nil, due to minimum leakage from the circuit. Its efficacy in preventing pulmonary relapse remains to be demonstrated.

KEY WORDS: lung metastases, sarcoma, hyperthermic isolated perfusion.

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