Quality of Life Evolution after Pulmonary Metastasectomy

A Prospective Study Comparing Isolated Lung Perfusion with Standard Metastasectomy

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Objective: To prospectively evaluate quality of life (QoL) evolution after a classic pulmonary metastasectomy or after an isolated lung perfusion (ILuP) metastasectomy.

Methods: QoL was prospectively recorded in 35 consecutive patients (27 classic metastasectomy; 8 ILuP) The European Organisation for Research and Treatment of Cancer C30 and lung cancer -13 QoL Questionnaires were administered before surgery and 1, 3, 6 and 12 months postoperatively (MPO).

Results: After a classic metastasectomy, a temporary increase in dyspnea (1 MPO $p = 0.03$ 3 MPO $p = 0.01$), coughing (3 MPO $p = 0.01$), fatigue (1 MPO $p = 0.01$, 3 MPO $p = 0.02$), thoracic pain (1 MPO, $p = 0.02$), shoulder dysfunction (1 MPO $p = 0.03$, 3 MPO $p = 0.02$) as well as an impaired physical (1 MPO $p = 0.01$, 3 MPO $p = 0.04$) and role functioning (1 MPO $p = 0.01$, 3 MPO $p = 0.01$) was reported the first 3 months after surgery. Six months after surgery, all domains returned to baseline. After ILuP metastasectomy, all QoL functioning and symptom scores, except for coughing complaints (1 MPO $p = 0.03$, 3 MPO $p = 0.04$) and shoulder dysfunction (1 MPO $p = 0.04$, 6 MPO $p = 0.04$), returned to baseline at 1 month after surgery. No significant differences were seen when QoL evolution was compared between classic and ILuP metastasectomy with the exception of a higher burden of thoracic pain (6 MPO $p = 0.04$, 12 MPO $p = 0.01$), shoulder dysfunction (6 MPO $p = 0.04$, 12 MPO $p = 0.02$), and dysphagia (6 MPO $p = 0.04$, 12 MPO $p = 0.02$) 6 and12 months after ILuP.

Conclusions: All QoL domains returned to baseline at 6 months after a classic metastasectomy. After ILuP, only increases in coughing and shoulder dysfunction were reported. In comparison classic metastasectomy patients, ILuP patients report more thoracic pain, shoulder dysfunction, and dysphagia.

Key Words: Quality of life, European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-C30, QLQ Lung Cancer-13, Lung metastases, Pulmonary metastasectomy, Isolated lung perfusion.

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Pulmonary metastasectomy has become a standard treatment for selected patients with different primary malignancies including colorectal and renal cell carcinoma. Even after complete surgical resection of pulmonary metastases, many patients develop recurrent disease in the thorax despite the use of systemic chemotherapy, the dosage of which is limited because of systemic toxicity. Although subsequent operations are feasible and good long-term results have been reported, sufficient functional lung parenchyma must remain. For this reason, new treatment strategies are being explored.

Similar to isolated limb and liver perfusion, isolated lung perfusion (ILuP) is a promising surgical technique for the delivery of high-dose chemotherapy with minimal systemic toxicity. ILuP with high-dose chemotherapy has proven to be highly effective in the experimental models of pulmonary metastases with a superior survival advantage compared with systemic treatment.[1–3] Phase I human studies have shown that ILuP is technically feasible with low morbidity and without compromising the patient's long-term pulmonary function.[4–6]

In addition to the impact on morbidity and mortality, new techniques in medicine need to be evaluated with regard to their effect on a patient's quality of life (QoL). Limited information is available regarding the long-term QoL evolution of patients who underwent a pulmonary metastasectomy. The objective of the present study is to measure long-term QoL evolution after pulmonary metastasectomy and to compare QoL after ILuP metastasectomy and classic metastasectomy.

PATIENTS AND METHODS

From January 2005 to December 2008, 35 consecutive patients who underwent a pulmonary metastasectomy were included in a prospective QoL evaluation. Eight of the 35 patients underwent isolated lung perfusion (ILuP) with melphalan as part of a phase I trial.[5] Patients with pulmonary metastases from melphalan-sensitive tumors were included in the phase I ILuP study if general and specific criteria were met. General criteria to perform a procedure were fourfold: metastatic disease assessed by radiologic examination was resectable, metastatic disease was confined to the lungs, patients had adequate pulmonary and cardiac reserve, and no comorbid conditions that preclude an operation were present. Exclusion criteria were pregnancy or lactation, uncontrollable infectious disease, liver or kidney insufficiency, severe

comorbidity, and previous thoracotomy or pleuropulmonary disease resulting in obliteration of the pleural space.[5] The QoL evolution of those patients was prospectively compared with that of 27 patients who underwent a classic metastasectomy. Patients of the extension trial with hyperthermic melphalan infusion were not included in the present study.[7] To obtain a more homogenous group, only patients operated in the Antwerp University Hospital, who underwent a pulmonary metastasectomy by anterolateral muscle-sparing thoracotomy were included. Patients who underwent a metastasectomy by video-assisted thoracic surgery or who underwent a synchronous or metachronous hepatic metastasectomy were excluded from the analysis. Further exclusion criteria were age younger than 18 years, mortality during the 12-month follow-up period, and previous thoracic surgery, The QoL and phase I ILuP study were approved by the ethics committee of the Antwerp University Hospital, and written informed consent was obtained from all patients.

QoL was prospectively recorded using the Dutch version of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 (cancer core questionnaire)[8] and the EORTC QLQ-Lung Cancer (LC)13 lung cancer-specific questionnaire module.[9] The EORTC QLQ-C30 is a self-rating questionnaire composed of 30 questions/items and incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea/vomiting), a global health/QoL scale, and several single items assessing additional symptoms (dyspnea, sleep disturbance, constipation, and diarrhea). A final item evaluates the perceived economic consequences of the disease.[8] The EORTC QLQ-LC13 is a supplementary questionnaire module and contains 13 questions/items assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), chemotherapy/radiotherapy-related side effects, and pain medication.[9] Reliability and validity of the EORTC QLQ-C30 and LC-13 questionnaires have been confirmed in international cancer studies.[8,9] The questionnaires were administered 1 day before surgery and at 1, 3, 6, and 12 months postoperatively (MPO). The questionnaires were sent to the patients by mail, accompanied by a letter with general information and the aim of the study.

Statistical analysis was performed using statistical software (SPSS, version 18.0, Chicago, IL). In accordance with procedures recommended by the EORTC, scores were linearly converted to a scale ranging from 0 to100 for each patient. For the global health/QoL and functional scales, higher scores represent a higher level of functioning. For the symptom scales, higher scores represent a greater symptom burden.[8,9] Parametric and nonparametric data were reported as mean and median, respectively. The Wilcoxon signed rank test was used to compare the mean value before and after surgery. A Student's *t* test was used to compare parametric data between groups. The Mann-Whitney *U* test and the Kruskall-Wallis test were performed to compare nonparametric data. The *p* value was considered statistically significant if 0.05 or lower.

Surgical Procedure of Isolated Lung Perfusion

Patients were intubated with a double-lumen endotracheal tube and underwent an antero- or posterolateral thoracotomy in a standard fashion. After inspecting the thoracic cavity, contraindications for a complete metastasectomy were excluded. All nodules were palpated before perfusion, and their anatomic localization was documented before perfusion. In case no preoperative histologic diagnosis was present, frozen section of one of the tumor nodules was performed to obtain pathologic confirmation of metastatic disease. Next, the main pulmonary artery and both pulmonary veins were isolated. The pericardium was opened to clamp the pulmonary artery and veins centrally. The patient was systemically anticoagulated. The pulmonary vasculature was clamped proximally and cannulated and the main bronchus was snared to occlude bronchial arterial blood flow. ILuP with melphalan was carried out for a period of 30 minutes with the use of a perfusion circuit. During the ILuP, the lung was ventilated. At the end, air was removed from the lung and pulmonary veins by sequentially removing the pulmonary artery cannula, repairing the arteriotomy, removing the cannulas from the pulmonary veins, and removing the pulmonary artery clamp until bleeding from the pulmonary veins had vented all the air. The venotomies were repaired and the clamps removed, restoring blood flow to the lung. After correcting the activated clotting time, a complete metastasectomy was performed. Metastases were resected with a margin of 5 mm of normal lung tissue. Subsequently, a hilar and mediastinal nodal sampling was performed.[5] Morbidity, in-hospital mortality, and long-term mortality of ILuP were recently published.[5,6]

RESULTS

Table 1 outlines patients' characteristics for the classic and the ILuP metastasectomy group. Table 2 shows the characteristics of the surgical procedure and postoperative recovery in the two groups. No significant differences were seen in characteristics of patients and surgical procedure when the two groups were compared, with the exception of a significant smaller diameter of the resected specimen in the ILuP group ($p = 0.04$). Both groups had a comparable response to the QoL questionnaire (Table 3). No significant differences in response rate were seen when the two groups were compared. Regarding response rate, 21 patients (60.0%) responded to all five questionnaires, five (14.3%) to four, four (11.4%) to three, and five (14.3%) to two of the questionnaires. There were no significant clinicopathological and baseline QoL differences between patients who responded to all questionnaires and those who did not.

Preoperative QoL

In general, most patients had a moderately impaired global well being, role, social and emotional functioning at baseline. Preoperatively, patients reported a burden of fatigue, sleep deprivation, and loss of appetite. No significant differences of QoL scores at baseline were seen between the classic and the ILuP metastasectomy groups. QoL at baseline for both metastasectomy groups is shown in Tables 4 and 5.