Whole Lung Irradiation in Patients with Exclusively Pulmonary Metastases of Ewing Tumors

Toxicity Analysis and Treatment Results of the EICESS-92 Trial

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Background: In the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS) 92, whole lung irradiation (WLI) was performed in patients with primary lung metastases. This retrospective analysis evaluates the pulmonary function and the outcome of patients with exclusively pulmonary metastases.

Patients and Methods: Between 1990 and 1999, 99 patients were registered into the EICESS-92-study trial with exclusively pulmonary metastases of Ewing tumors. The multimodal treatment regimen included polychemotherapy and local therapy to the primary tumor. WLI was performed with a dose between 12–21 Gy. 70 patients were treated with WLI, 13 of them received a further boost to their primary tumor in the thorax up to a cumulative dose of 54 Gy.

Results: Pulmonary function tests were available for 37 patients treated with WLI (± boost). None, mild, moderate or severe pulmonary complications were seen in 43%, 29%, 21% and 7% of patients treated with WLI without further boost (median follow-up 25.2 months). Patients with an additional radiation boost or surgery to the thorax showed slightly higher rates of complications. Overall survival (OAS) showed a trend towards better results for patients with WLI (5-year-OAS: 0.61 for WLI vs. 0.49 for no WLI, p = 0.36).

Conclusion: These data indicate a benefit and acceptable toxicity for WLI in the presented collective of patients. As long as there is no randomized prospective analysis, the present data confirm the indication for WLI in Ewing tumor patients with primary exclusively lung metastases.

Key Words: Ewing tumor · Whole lung irradiation · Toxicity · Outcome

Ganzlungenbestrahlung bei Patienten mit ausschließlicher Lungenmetastasierung von Ewing-Tumoren. Toxizitätsanalyse und Behandlungsergebnisse der EICESS-92-Studie

Hintergrund: In der European Intergroup Cooperative Ewing’s Sarcoma Study (EICESS) 92 wurde bei Patienten mit primären Lungenmetastasen eine Ganzlungenbestrahlung durchgeführt. Für diese retrospektive Analyse wurden Lungenfunktion und Behandlungsergebnisse von Patienten mit ausschließlich pulmonaler Metastasierung analysiert.


Ergebnisse: Lungenfunktionsanalysen waren bei 37 Patienten mit Ganzlungenbestrahlung (+ Boost) zu erheben. Keine, milde, moderate oder schwere pulmonale Einschränkungen waren in 43%, 29%, 21% und 7% der Patienten mit alleiniger Ganzlungenbestrahlung zu erheben (mediane Nachbeobachtungszeit 25,2 Monate) (Tabellen 2 und 3: Vergleich der Patientencharakteristika von Patienten mit/ohne Funktionseinschränkungen (Tabelle 2) bzw. mit/ohne Lungenfunktionsprüfung im Verlauf (Tabelle 3). Patienten mit einem zusätzlichen Boost oder einer Operation am Thorax (Tabelle 1) zeigten etwas höhere Komplikationsraten. Im Trend zeigte das Gesamtüberleben für die Patienten, die eine Ganzlungenbestrahlung erhalten hatten, bessere Ergebnisse (Abbili...
Introduction
Multimodal therapy including polychemotherapy, surgery and radiotherapy has resulted in survival rates of more than 60% for patients with Ewing tumors without metastases at the time of initial diagnosis [11, 19]. The clinical outcome for children with metastatic disease is generally poor [14]. However, patients with metastases restricted to the lungs reportedly have a somewhat better prognosis than patients with extrapulmonary metastases [7, 12, 15].

In the European Intergroup Cooperative Ewing's Sarcoma Study (EICESS-92), whole lung irradiation (WLI) was performed in all patients with primary pulmonary metastases, even when complete clinical remission had been obtained following polychemotherapy. Some data indicate a benefit of this therapy [7, 15, 23, 25]. Analyses of patients receiving WLI for pulmonary metastasized Ewing tumors have focused on the impact of WLI on the survival of the patients. Currently no valid data are available regarding pulmonary function impairment. Radiation-associated late effects are of major interest [3–6, 10, 13, 17] as they are of fundamental importance in discussions regarding risk-benefit considerations. The present analysis focuses on toxicity and treatment results of WLI for patients with exclusively pulmonary metastases of Ewing tumors.

Patients and Methods
The patients included in this analysis had histologically confirmed Ewing tumors with pulmonary metastases at diagnosis without extrapulmonary metastases. The treatment evaluation for this analysis was based on the EICESS-92 study database.

In EICESS-92, 14 courses of VAIA (vincristine, doxorubicin, ifosfamide, actinomycin D) or EVAIA (VAIA plus etoposide) chemotherapy were randomly applied in high risk patients, defined as patients with a primary tumor volume > 100 cm³, or metastatic disease [19]. All patients with pulmonary metastases reported here were defined as high-risk patients. Local therapy was performed as described elsewhere [18–21]. WLI was recommended in patients with pulmonary metastases at diagnosis even if a complete remission had been achieved after chemotherapy. In patients with incomplete pulmonary remission following chemotherapy, surgical removal of the remaining lung disease prior to radiotherapy was performed where feasible. WLI was scheduled in week 31 from start of therapy, paralleling the 11th course of chemotherapy. The recommendation was to irradiate both lungs using opposed ap/pa photon fields to a dose of 15 Gy (for patients < 14 years of age) or 18 Gy (patients > 14 years). However, bilateral whole lung irradiation was administered with doses between 12–21 Gy in the collective of the present patients. The daily fraction was either 1.5 Gy once daily or 1.25 Gy twice daily (lung dose). The dose calculation was based on CT-planning (prescribed to the 100% isodose) or had to consider the lung correction factor in case of central beam calculation. Patients with a primary tumor of the chest wall or thoracic vertebrae received a further boost to a total dose up to 54 Gy to the primary tumor area in some cases. Detailed information regarding dose-volume histograms of these patients was not available. Radiotherapy to the lungs was performed between January 1991 and August 2000. An independent trial radiotherapy reference center made recommendations for radiation portals, doses, and application of WLI or further boost irradiations. Additional details concerning local and systemic therapy have previously been published [9, 18–21].

In January 2006, the pediatric oncology institutions which had included patients into the trial were asked for results of pulmonary function tests (PFTs) of patients who had received whole lung irradiation. For interpretation of PFTs results for this report, individual PFT results were graded as mild, moderate or severe according to the PFT-investigators’ comments. Grade 0 was defined as pulmonary function test without any pathologic result, grade 1, 2 and 3 were defined as mild, moderate and severe pulmonary function abnormality. Protocols for the performance of spirometry, body plethysmography, and diffusing capacity are given by the American Thoracic Society [1]. This grading is also used by others to achieve standardization for PFT result examination [24]. Event-free (EFS) and overall-survival (OAS) were estimated using the Kaplan-Meier method. Progression during therapy, local or metastatic relapse, new metastases, second tumors, and death for any reason observed as first events were regarded as end points for EFS; death for any reason was regarded as end point for OAS analyses, comparison between groups were done by logrank statistics. To reduce a selection bias between both groups (± WLI), patients without WLI due