5. SUMMARY

Drug resistance is one of the main challenges to overcome in cancer treatment. There are three known major factors conveying multidrug resistance: P-glycoprotein, encoded from the mdr1 gene; multidrug resistance protein 1 (MRP1), encoded from the mrp1 gene and the vaults, with the lung resistance protein (LRP) encoded from the lrp gene as their chief component. Recently, LRP has been identified as an independent and superior predictive factor for drug resistance in vitro compared with P-glycoprotein and MRP1. Induction of the drug resistance had been observed in patients not only after therapy with cytotoxic drugs, but also after radiotherapy. However, these findings are from rather small studies. In the modern management of malignant diseases, the combined approach of chemotherapy and radiotherapy is often used and the understanding of potential radiation – induced multidrug resistance could prove essential for the design of schedules for maximal therapeutic effect.

The current study presents a thorough evaluation of the P-glycoprotein, MRP1 and LRP expression on gene and protein level in relation to irradiation, using a fractionated irradiation protocol identical to a commonly used protocol for treatment of tumor patients. The investigation was complemented by chemosensitivity assays with the cytotoxic agents bendamustine, cisplatin and doxorubicin. Evaluated were eleven cell lines of breast and colon cancer, which are most frequently treated with combined radio-chemotherapy protocols. The present work reports of significant overexpression of P-glycoprotein, MRP1 and LRP on gene and protein level following fractionated irradiation. This observation was paralleled by chemoresistance to clinically relevant concentrations of bendamustine, cisplatin and doxorubicin. Furthermore, correlation between the overexpression of P-glycoprotein, MRP1 and the resistance to bendamustine and doxorubicin was detected. It should be noted that the P-glycoprotein and MRP1 overexpression as well as the simultaneous chemoresistance were still present to some degree as late as 18 days after the last irradiation. In conclusion, this investigation demonstrates that fractionated gamma-irradiation frequently induces overexpression of P-glycoprotein, MRP1 and LRP and might be the cause of the concomitant chemoresistance

to structurally non-related cytotoxic drugs following radiation therapy, which is important for the development of radio-chemotherapeutic protocols.