Clinical and Molecular Studies of Liposarcoma

Department of Oncology, Institute of Clinical Sciences, and
Lundberg Laboratory for Cancer Research at the Department of Pathology,
Sahlgrenska Academy, Göteborg University, Sweden

AKADEMISK AVHANDLING

som för avläggande av medicine doctors examen vid Göteborgs Universitet kommer att offentligen försvaras
i sal Arvid Carlsson, Medicinaregatan 3,
måndagen den 11 juni 2007, kl 13:00

Katarina Engström, leg. läkare

Fakultetsopponent:

Professor Carl Blomqvist
Uppsala universitet, Uppsala

Avhandlingen baseras på följande delarbeten:

I Katarina Engström, Peter Bergh, Pelle Gustafson, Ragnar Hultborn, Helena Johansson, Rickard Löfvenberg, Kirsten Sundby Hall, Clement Trovik, Ola Wahlström, Henrik C,F. Bauer.

Liposarcoma – outcome based on 237 patients from the Scandinavian Sarcoma Register. *Manuscript.*

II Katarina Engström, Peter Bergh, Claes-Göran Cederlund, Ragnar Hultborn, Helena Willén, Pierre Åman, Lars-Gunnar Kindblom, Jeanne M. Meis-Kindblom.

Irradiation of myxoid/round cell liposarcoma induces volume reduction and lipoma-like morphology. *Acta Oncol 2007, 22 January: DOI:10. 1080/02841860601080415.*

III Katarina Engström, Helena Willén, Christina Kåbjörn-Gustafsson, Carola Andersson, Marita Olsson, Melker Göransson, Sofia Järnum, Anita Olofsson, Elisabeth Warnhammar, Pierre Åman.

The myxoid/round cell liposarcoma (MLS/RCLS) fusion oncogene *FUS-DDIT3* and the normal *DDIT3* induce a liposarcoma phenotype in transfected human fibrosarcoma cells. *Am J Pathol 2006, 168:5.*

IV Anita Olofsson, Helena Willén, Melker Göransson, Katarina Engström, Jeane Meis-Kindblom, Göran Stenman, Lars-Gunnar Kindblom, Pierre Åman.

Abnormal expression of cell cycle regulators in FUS-CHOP carrying liposarcomas. *Int J Oncology 2004, 25:1349-1355.*

ABSTRACT

Clinical and Molecular Studies of Liposarcoma

Katarina Engström, Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, Göteborg University, Sweden

Aims: (1) To analyse clinicopathological characteristics, treatment and outcome of liposarcoma, and to determine how the Scandinavian Sarcoma Group (SSG) treatment guidelines were followed; (2) to analyse tumour volume and morphology response after radiotherapy in myxoid/round cell liposarcoma (MLS/RCLS); (3) to examine the role of the MLS-specific fusion gene *FUS-DDIT3* in development of liposarcomas; and (4) to analyse expression patterns of cell cycle regulating proteins in MLS.
Methods: (1) A total of 319 liposarcomas reported between 1986−1998 to the SSG Register were reviewed. Altogether 237 patients without initial metastasis were analyzed for local recurrences in relation to surgical margins and radiotherapy, metastasis and survival. (2) Thirty-three primary or metastatic MLSs/RCLSs were treated with radiotherapy. Tumour size was measured by MRI or CT. Histopathology was performed of both non-irradiated and irradiated lesions. (3) The fibrosarcoma cell line HT1080 was transfected with the recombinant vectors p*FUS-DDIT3*-EGFP, p*DDIT3*-EGFP and p*FUSa*-EGFP. The tranfectants and the HT1080 cell line were injected into SCID mice, followed by histopathology. The transfected and non-transfected cells were cultured with adipogenic induction medium and microarray-based expression comparison of the different cell lines was performed. (4) Cell cycle controlling factors were analyzed by immunohistochemistry and Western blotting in non-irradiated and irradiated MLSs/RCLSs.
Results: 1) Altogether 78% were primarily operated at a sarcoma centre, 45% with wide margins. Only 58% of high-grade (Grades III-IV) lesions with non-wide surgery had postoperative radiotherapy. The risk of local recurrence in this group was 47%, if not irradiated. The estimated 10-year local recurrence-free and metastasis-free survival in the low-grade (Gades I - II) group was 87% and 95% respectively, while in the high-grade group it was 75% and 61%, respectively. Independent adverse prognostic factors for local recurrence were surgery outside a sarcoma centre and dedifferentiated liposarcoma. For metastases, they were old age, large tumour size, high grade and histological type MLS /RCLS. (2) Irradiated MLS/RCLS showed median tumour volume reduction of 52% in 23 tumours. The morphology showed paucicellularity, hyalinization, and lipoma-like appearance. There were no obvious differences in volume reduction or morphologic response in MLSs/RCLSs in comparison with MLSs. (3) Cells expressing *FUS-DDIT3* and *DDIT3* grew in SCID mice as liposarcomas and the capillary network was similar to that found in MLSs/RCLSs. Cells transfected with *DDIT3* responded in vitro to adipogenic factors by accumulation of fat, and microarray-based comparison showed that the *DDIT3* and *FUS-DDIT3* transfected variants shifted toward an MLS/RCLS-like expression pattern.
(4) High expression of cyclin D1 and E, their kinases and kinase-inhibitors P16, P27 and P57 was observed together with low Ki67 and normal cyclin A.
Conclusion: Liposarcoma should be treated at specialized centres and postoperative radiotherapy is indicated for high-grade lesions, at least after non-wide surgery. Low-grade MLSs have high radio-responsiveness and radiotherapy is indicated after non-wide surgery or in a preoperative setting. The fusion oncogene *FUS-DDIT3* and *DDIT3* may induce a liposarcoma phenotype with *DDIT3* being the tumour type-determining part. Deregulation of G1 controlling proteins is common and indicates that MLS cells accumulate in late G1 phase.

Key words: Liposarcoma, radiotherapy, prognostic factors, transfection, *FUS-DDIT3*, adipogenesis, microarray expression analysis, cell cycle, immunohistochemistry.
ISBN 978-91-628-7193-2