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Chapter 7

Summary, discussion and concluding remarks
This thesis presents the clinical characteristics and prognostic factors in patients with low-grade cartilaginous tumours diagnosed in the context of Ollier disease and Maffucci syndrome (chapter 2). And beyond, we focus on therapeutic options concerning the cytotoxic (chapter 3) and pharmacological (chapter 4) effects of phenol, and the clinical use of phenol as adjuvant therapy following intralesional curettage of an atypical cartilaginous tumour (ACT)/low-grade central chondrosarcoma of long bones (chapters 5 and 6).

In chapter 2, a European retrospective multicenter study was performed to gain more insight in the presentation and characteristics of enchondromas in patients with Ollier disease and Maffucci syndrome. Furthermore, we tried to estimate the cumulative risk of secondary transformation of enchondroma over a lifetime looking for variables significantly associated with outcome and mortality. Data were collected by members of the European Musculoskeletal Oncology Society (EMSOS), a multidisciplinary society with special interest in bone and soft tissue tumours. 161 Patients were included. The overall incidence for developing chondrosarcoma was 40%, but may increase when considered as a lifelong risk due to age-dependency. Patients with enchondromas located in long bones or axial skeleton, especially the pelvis, have seriously increased risk of developing chondrosarcoma. Based upon this study, they are identified as the population that needs regular screening on early signs of malignant transformation.

Several studies were performed alongside to investigate phenol, an etching acid, that already was used for a long period in the surgical treatment of bone tumours. In chapter 3, the cytotoxicity of phenol on different cell-lines was described. Due to the fact that ethanol is standardly used during surgery to rinse phenol after application at the bone, ethanol was also assessed to sort out its separate potential cytotoxic effect. Two different cell-lines were used for these in vitro experiments. First SiHa, a cervical carcinoma cell line was used as a non-specific control. Secondly, we used OUMS-27, a human chondrosarcoma-derived cartilage producing cell line. End point of the test was cell death, measured by flow cytometry.

A first set of experiments on the SiHa cell line was used to detect the effective range of concentrations of phenol (0-10.63%) and ethanol (0-96%). In the second set, 14 different concentrations of phenol were tested in a range from 0.2% up to 1.5%. In ethanol, the second test was performed with 14 different concentrations from 10% up to 45%. All cells were killed with 1.5% phenol and 42.5% of ethanol. The
experiments were repeated four times. All five results were comparable. In these experiments, we showed that both phenol and ethanol have the ability to kill chondrosarcoma cells in vitro. By using flow cytometry, we did not focus on the necrotising effect, but instead investigated how phenol and ethanol impair tumour-cell viability.

In the past, various studies demonstrated that by using an adjuvant in the intralesional treatment of bone tumours, the results of local treatment were greatly improved. Despite the use of phenol for a long time as adjuvant during surgery, hardly no studies were performed on details of local achieved concentrations of phenol. Subsequently, the number of times you need to rinse the bone cavity with ethanol to dilute phenol to an acceptable concentration. In chapter 4, we present two studies. In the first study (test 1, n=16), we collected 10 samples (1 to X) of a mixture of phenol/ethanol solution, while rinsing the applied phenol with ethanol 96%. In the second study (test 2, n=10), we collected 10 samples from the bone cavity with a mixture of phenol/ethanol solutions. Biopsy A was taken after applying phenol 85% on the inner surface of the cavity wall, biopsy B was taken after rinsing the cavity ten times with ethanol 96%.

The phenol concentration of the ethanolic flush solution was determined by High Performance Liquid Chromatography (HPLC) with spectrophotometric detection. The studies showed that rinsing the cavity five times already gives a phenol concentration <280 ppm, which is considered to be a safe dose. The volume of the cavity had no correlation with the measured concentrations of phenol.

This study shows that the potential adverse effects of phenol in the treatment of patients can be reduced by using ethanol to wash out phenol to safe concentrations.

In chapter 5, a retrospective analysis was presented of 85 patients who had been treated in a specialized musculoskeletal oncology department for an ACT/grade I central chondrosarcoma of a long bone.

The indication for surgery was the likely presence of an ACT/grade I central chondrosarcoma on the Gd-MRI scans, located in one of the long bones. Surgery was performed by intralesional curettage, application of phenol, rinsing with ethanol, and bone-grafting. Patients were scheduled for a dynamic Gd-MRI scan six to twelve months after the procedure and then biannually.

The average duration of follow-up for the patients was 6.8 years (range, 0.2 to 14.1 years). Five patients had a follow-up of less than two years. Eleven patients underwent repeat intervention due to a suspicious lesion on the Gd-MRI studies during
follow-up. Depending on the size of the lesion, treatment by radiofrequency ablation or re-curettage was performed. Of these eleven, five had a histologically proven local recurrence (5.9% [95% CI 0.9-10.9%]).

The use of phenol as an adjuvant as described in this study has potential advantages for the patients. In contrast to other adjuvants, adjacent joints are not impaired by this procedure. Due to the fact that we did not need to plate long bones to prevent fractures, Gd-MRI scans could be used in the follow-up of these patients group.

Finally, in chapter 6, a study was presented concerning postoperative features on Gd-MRI after curettage and application of phenol in ACT/grade I central chondrosarcoma in long bones. Intralesional curettage with the use of a local adjuvant is state of the art in the therapy for ACT/grade I central chondrosarcoma nowadays. The role of preoperative conventional radiographs and magnetic resonance (MR) imaging is well established. However, there is still limited literature on the postoperative findings on MR imaging. There are only small series available, containing a large variety of diagnosis, surgical approach and use of different adjuvant therapies.

Purpose of this retrospective study was to identify features on MR imaging of local residual or recurrent disease, besides normal postoperative changes after surgery.

Between 1994 and 2005, we included 75 patients with histologically proven ACT/grade I central chondrosarcoma of long bones. Preoperative plain radiographs in two directions and a Gadolinium-MR imaging were performed. Postoperative plain radiographs were performed before discharge, at 6 weeks and at one year. Gd-MR imaging was performed 6-12 months after surgery, and subsequently biannually.

Concerning plain radiographs, complete consolidation of the bone window was observed in all patients. Two patients suffered from a femoral fracture within 6 weeks of surgery. In our series, no patients showed any abnormalities, suspected for local recurrence.

On the basis of the results of the postoperative Gd-MR images of 75 patients, we could identify four groups, describing the increasing risk for recurrence of the tumour. Group 1 showed normal postoperative changes without any suspicion for residual or recurrent tumour on all postoperative MR images (54%). Group 2 showed nodules within the granulation zone, diminishing in size during follow-up (24%). Group 3 showed nodules, which size stayed stable or increased in time (17%). Group 4 first showed normal aspect of the granulation zone, but in time MR imaging showed the development of a new Gd-enhancing lesion suspicious for local recurrence during follow-up (5%).

A second operation was performed in 14 patients due to radiological suspicion of
residual or recurrent tumour on Gd-MR imaging. Depending on the size of the lesion, radiofrequency ablation (<10 mm) or curettage (≥10 mm) was performed. Histological examination proved eight local recurrences.

Due to new insights during this study in combination with the recent experiences in the treatment of this patients group, this resulted in a flow-chart for the follow-up of patients suffering from ACT/grade I central chondrosarcoma of long bones (see figure 6, page 101).

**General discussion**

Ollier disease and Maffucci syndrome are rare disorders, with great impact on a patient’s life. Besides the discomfort due to limb length discrepancies and deformities of hands and/or feet, the uncertainty of the fact that each of the dozens of enchondroma can one day transform to a chondrosarcoma, is hard to live with, not only for the (young) patient, but also for their parents and relatives.

Therefore, we performed a study to get more insight in the clinical behaviour of enchondromas in these two disorders.

Disadvantages are that the study is retrospective in design, and the patients are not followed in a cohort until death. Also, there is a selection bias due to the fact that our data were mainly collected from referral centers for musculoskeletal oncology. This may have lead to overestimation of the percentage of developing chondrosarcoma grade I-III.

Nevertheless, the study we performed and presented in chapter two contributes to the understanding of the clinical behaviour of enchondroma in patients suffering from Ollier disease or Maffucci syndrome.

To estimate the cumulative probability of secondary transformation over a lifetime, it is important to distinguish the distribution patterns of enchondroma. When enchondroma are found in the axial skeleton or long bones, (group II and III), the risk for developing chondrosarcoma is 44-50%. The odds ratio associated with secondary chondrosarcoma of the pelvis was 3.8 (95% CI 1.8-8.0, p= .001).

On plain radiographs and MR images enchondromas in Ollier disease and Maffucci syndrome usually show a more aggressive picture than in solitary ACT/grade I chondrosarcoma. In general they still might be benign and therefore markers as growth and progression in time should be investigated before a biopsy is planned, to prevent misleading outcomes of the biopsy.

Due to the fact that both Ollier disease and Maffucci syndrome are associated with
a variety of other malignant tumours in the brain and abdomen, a cerebral or abdominal CT-scan should be performed with minimal neurological complaints or abdominal symptoms.

Throughout this thesis, one should read the different studies concerning phenol being aware of new insights in time, in which also the general accepted terminology changed (WHO 2012).

The treatment of ACT/grade I central chondrosarcoma has remarkably changed in the last three decades. Where till 1990 the common therapy was wide resection, therapy changed towards intralesional curettage followed by adjuvant therapy, or even watchfull waiting. The small chance of dedifferentiation of the lesions remains a concern.

This change in the approach towards the extend of surgical resections were made, was mainly based on two developments. The first was a better understanding of the behaviour of low-grade chondrosarcoma, regarding to the work done studying molecular genetics and histopathology. Clinical studies proved that no patients died as a result of ACT/grade I central chondrosarcoma of long bones, treated by intralesional curettage and the use of an adjuvant. The second was the upcoming role of Gd-MRI. Thanks to the use of Gd-MRI in different benign and malignant bone tumours, the positive predictive value for identifying malignant transformation increased in time.

This thesis contributed to the scientific foundation of the clinical use of phenol. Studies in the past always had discussions about the cell killing potentials of phenol, where endpoint for effectiveness of adjuvant was the measurable depht of necrosis. Due to the fact that phenol is very corrosive, the cells vanish. By using flow cytometry, cell pyknosis was proven in very low concentrations of phenol. Also, the separate and own effect of ethanol was proven in this thesis.

The clinical study in chapter 5 should also be judged in the timeframe. When we started to include the patients in 1994, many countries in Europe still treated this patients group with wide resections and reconstructions. This is why, already in case of little suspicion on residual or recurrent chondrosarcoma, we performed a new procedure.

Nowadays, in the Leiden University Medical Center, curettage, phenol cauterization and bone grafting is indicated in case the cartilage lesion is > five centimeter, in case of endosteal scalloping, enhancement of the lesion within 10 seconds on Gd-MR imaging or age of onset is > 50 years.

The patient is involved in the decision whether to plan an intervention or to wait and see, in the knowledge that the patient stays in the follow-up with periodically
planned MRI scans. In case the MRI shows edema around the lesion, periostal edema or periostal reaction, a biopsy will be planned, to be sure no grade II chondrosarcoma is developing. The developments in the wider use of radiofrequency ablation (RFA) are promising. Dierselhuis and Jutte recently published a small series of patients with enchondroma and ACT’s < 3 cm's who were first treated with radiofrequency ablation, and had curettage afterwards to judge the percentage of necrosis of the lesion. In the near future, studies should be performed on uni-probe and/or multi-probe radiofrequency ablation in one to three sessions in daycare, followed by MR imaging, not only in small lesions, but also in ACT/grade I chondrosarcoma <5 cm. The future is to develop a prediction model, in which an individual risk model can be designed for each patient according to the growth or progression of a lesion suspected for enchondroma/ACT. In the next decades, this model will give more insight in the natural behaviour of these premalignant lesions, and lead to evidence based on shared decision making. It will create the optimal balance between safety, uncertainty and surgical risks you will or will not expose the patient to.