SUMMARY

This thesis focuses on two distinct aspects of the rare pediatric eye disease retinoblastoma: first, retinoblastoma imaging with magnetic resonance imaging (MRI) and second, epidemiology and imaging of trilateral retinoblastoma.

Part I: retinoblastoma imaging

The first five chapters are about radiological imaging of retinoblastoma, with the first chapter systematically reviewing available literature on the diagnostic performance of MRI and computed tomography (CT) for the diagnosis of tumor extent (e.g., optic nerve invasion and choroidal invasion) in advanced retinoblastoma.¹ The diagnostic gold standard for the detection of these risk factors is histopathologic analysis, but histopathologic analysis is only available after enucleation of the affected eye. Increasingly eyes with advanced-stage retinoblastoma are treated with conservative eye-sparing regimens emphasizing the importance of non-invasive imaging. Chapter 1 includes literature published until April 2013 assessing the diagnostic performance of MRI and CT in detecting intra- and extraorbital tumor extension of retinoblastoma. In total 14 studies on MRI (591 eyes) and 4 studies on CT (257 eyes) were included. Meta-analysis resulted in a diagnostic accuracy of conventional MRI at detecting postlaminar optic nerve, choroidal, and scleral invasion with sensitivities of 59% (95% CI 37–78), 74% (95% CI 52–88), and 88% (95% CI 20–100), respectively and specificities of 94% (95% CI 84–98), 72% (95% CI 31–94), and 99% (95% CI 86–100), respectively. MRI with a high (versus a low) image quality showed higher diagnostic accuracies for detection of prelaminar optic nerve and choroidal invasion, but these differences were statistically not significant. There was insufficient data on the diagnostic accuracy of CT to perform a meta-analysis. In conclusion chapter 1 shows that MRI is an important diagnostic tool for the detection of local tumor extent in advanced retinoblastoma although its diagnostic accuracy has room for improvement, especially its sensitivity. Although the few available studies are old, chapter 1 also shows there is very little evidence regarding the diagnostic accuracy of CT. Generally these studies show low diagnostic accuracy.

Chapter 2 demonstrates the value of high-resolution MRI in diagnosing, staging, and follow-up of retinoblastoma during eye-saving treatment.² Retinoblastoma cases examined on a 3T system from a retrospective retinoblastoma cohort from 2009 through 2013 were included. The potential application of high-resolution MRI is demonstrated for the detection of small intraocular seeds, hemorrhage, metastatic risk factors like optic nerve invasion and choroidal invasion not visible with fundoscopy, and treatment response. Unfortunately, however, the diagnostic accuracy of high-resolution MRI is not perfect, especially for subtle intraocular seeds or minimal postlaminar optic nerve invasion.

The purpose of chapter 3 is to show the potential of ultrahigh-field (9.4T and 17.6T) MRI for detection of retinoblastoma tumor extent and depicting tumor morphology by using prospectively obtained in and ex vivo images.³ Six patients (median age 5.5 months, range 2–14) with retinoblastoma were prospectively included in this study. Prior to enucleation in vivo MRI was performed using a 1.5T system with a circular surface coil covering the eye. Ex vivo imaging was performed on two vertical 89-mm-bore magnets at field strengths of 9.4 T (400 MHz) and 17.6 T (750 MHz). After ex vivo imaging the eyes were histopathologically analyzed and matched with MRI findings. We were able to correlate ultrahigh-field MRI characteristics of various aspects of intraocular retinoblastoma (growth type, viable tumor...
versus necrosis and tumor seeding) with histology. Retinoblastoma with extensive necrotic areas and numerous viable pseudorosettes presents as an identical ‘geographical pattern’ on both MR and histopathology images. Finally we show MR images of tumor in close proximity to the choroid, but no invasion yet. This chapter showed the possibilities of ex vivo imaging of retinoblastoma with ultrahigh-resolution MRI for various aspects of disease staging. Additionally, it gives insight into small anatomical details and might reduce histopathological sampling error. Improved disease staging (in and ex vivo) with more detailed imaging can potentially improve treatment decisions.

In chapter 4 we investigate the correlation of intraocular retinoblastoma tumor size measured with MRI and postlaminar optic nerve invasion and massive choroidal invasion. For this multicenter study we were able to retrospectively include 370 consecutive retinoblastoma patients (375 eyes) from 1993 through 2014. ROC analysis of volume and diameter, respectively, yielded AUCs of 0.77 (95% CI 0.70–0.85, P<0.0001) and 0.78 (95% CI 0.71–0.85, P<0.0001) for postlaminar optic nerve invasion (n=375) and 0.67 (95% CI 0.57–0.77, P=0.0020) and 0.70 (95% CI 0.59–0.80, P=0.0004) for massive choroidal tumor invasion (n=219). For the detection of concurrent massive choroidal invasion and postlaminar optic nerve invasion (n=219), volume and diameter show AUCs of 0.81 (95% CI 0.70–0.91, P=0.0032) and 0.83 (95% CI 0.73–0.93, P=0.0016), respectively. Chapter 4 shows that intraocular tumor size is strongly associated with postlaminar optic nerve invasion and co-occurring postlaminar optic nerve invasion and choroidal invasion. A moderate association was found with massive choroidal invasion. These findings might prove to be potentially useful in a clinical setting, especially within the scope of increasing use of eye-salvage treatment strategies.

Orbital tumor recurrence is a rare but serious complication in children with retinoblastoma, which leads to a high risk of metastasis and death. The final chapter of part I (chapter 5) analyzes the diagnostic accuracy of high-resolution MRI to detect orbital tumor recurrence in children with retinoblastoma. Post-enucleation MR images of 50 children (55 orbits and 50 children) were analyzed. Imaging was performed with orbital surface coils at 1.5 T. Abnormal orbital enhancement was a common finding after enucleation (100% in the first three months after enucleation, 64.3% above three years after enucleation). All histopathologically confirmed tumor recurrences in 3 out of 55 orbits (5.5%) were correctly judged as “definitive tumor” in MRI. Two orbits from two children rated as “suspicious of tumor” received intravenous chemotherapy without histopathological confirmation; further follow-up (67 and 47 month) revealed no sign of tumor recurrence. In 90.2% no tumor was suspected on MRI, which was clinically confirmed during follow-up (median follow-up after enucleation 45 months (range 8–126). High-resolution MRI with orbital surface coils may reliably distinguish between common postsurgical contrast enhancement and orbital tumor recurrence, and may therefore be a useful tool to evaluate orbital tumor recurrence after enucleation in children with retinoblastoma. We therefore recommend high-resolution MRI as a screening tool for the orbit in children with retinoblastoma to exclude tumor recurrence, especially in high-risk patients (such as enucleations preceded by neoadjuvant therapy, buphthalmos and resection margins that are not certainly histologically tumor free) within the critical first two years after enucleation.
Part II: the pineal gland & trilateral retinoblastoma

We hypothesized that a trilateral retinoblastoma incidence – as previously published by Kivilä – of 5 to 15% was an overestimation. To find out to what degree the incidence was exaggerated, we estimated the incidence of trilateral retinoblastoma in patients with retinoblastoma in chapter 6. Scientific literature published between January 1966 and July 2015 that assessed trilateral retinoblastoma incidence was included. Twenty-three retinoblastoma cohorts from 26 studies were included in this study. For patients with bilateral retinoblastoma we found an unadjusted chance of developing trilateral retinoblastoma across all cohorts of 5.3% (95% confidence interval [CI]: 3.3–7.7%); the chance of pineal trilateral retinoblastoma was 4.2% (95% CI: 2.6–6.2%) and the chance of non-pineal trilateral retinoblastoma was 0.8% (95% CI: 0.4–1.3%). In patients with hereditary retinoblastoma (all bilateral cases, and the unilateral cases with a family history or a germline RB1 mutation) we found a trilateral retinoblastoma incidence of 4.1% (95% CI: 1.9–7.1%), and a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8–6.2%). To reduce the risk of overestimation bias we restricted analysis to retinoblastoma cohorts with a minimum size of 100 patients, resulting in adjusted incidences of 3.8% (95% CI: 2.4–5.4%), 2.9% (95% CI: 1.9–4.2%), and 0.7% (95% CI: 0.3–1.2%) for any, pineal and non-pineal trilateral retinoblastoma, respectively, among patients with bilateral retinoblastoma. Among hereditary retinoblastoma we found an adjusted trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2–6.7%) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4–5.6%). Chapter 6 shows that the estimated incidence of trilateral retinoblastoma is lower than what was usually reported in previous literature, especially after exclusion of small cohorts that were subject to overestimation bias in this context.

In chapter 7 we investigate the changes of patient survival over time and the factors that influence survival. Trilateral retinoblastoma cases published from January 1966 through April 2014 were included. Altogether, 174 trilateral retinoblastoma patients from 90 studies qualified for meta-analysis and were included. When comparing trilateral retinoblastoma diagnosed before and since 1995, 5-year survival after pineal and non-pineal trilateral retinoblastoma increased from 6% (95% CI 2–15) to 44% (95% CI 26–61; P<0.0001) and from no survivors to 57% (95% CI 30–77; P=0.035), respectively. Hazard ratios (HR) adjusted for the presence of leptomeningeal metastases and trilateral retinoblastoma location, suggested that both conventional (HR 0.059, 95% CI 0.016–0.226; P<0.0001) and high-dose chemotherapy with stem-cell rescue (HR 0.013, 95% CI 0.002–0.064; P<0.0001) most strongly contributed to this improvement. Absence of leptomeningeal metastases (HR 2.13, 95% CI 0.98–4.60; P=0.055) was associate with improved survival. Non-pineal trilateral retinoblastoma were larger than pineal tumors (median 30 [range 6–100] versus 22 mm [range 7–60]; P=0.012) but both had similar outcomes since 1995. Chapter 7 suggests that improved chemotherapy regimens and earlier detection of pineal trilateral retinoblastoma explain the improved overall survival. Successful trilateral retinoblastoma treatment should therefore include screening at least at the time of retinoblastoma diagnosis and chemotherapy, preferably a high-dose regimen with autologous stem-cell rescue.

Chapter 8 presents a patient diagnosed with unilateral familial retinoblastoma at the age of thirteen days. Nineteen months later MR images of the brain showed a suspicious cystic pineal gland. On a follow-up MR scan after another nine months this lesion was diagnosed as pineoblastoma. The tumor was resected and subsequently high-dose chemotherapy was given,
concluded with autologous stem-cell rescue. The patient was doing well at the last follow-up (almost 5 years after resection). The case from chapter 8, emphasizing the findings described in chapter 7, shows that if there is any suspicious finding concerning the pineal gland on brain MR images in retinoblastoma patients, follow-up scans are highly recommended.

Differentiation between normal solid (non-cystic) and cystic pineal glands and pineal pathologies on brain MRI proves to be difficult. The aim of chapter 9 is to assess the size of the solid pineal gland in children (0-5 years) and compare the findings with published pineoblastoma cases. We retrospectively analyzed the size (width, height, planimetric area) of solid pineal glands in 184 non-retinoblastoma patients (73 female, 111 male) aged 0–5 years on MRI. The effect of age and gender on gland size was evaluated. Linear regression analysis was performed to analyze the relation between size and age. Ninety-nine percent prediction intervals around the mean were added to construct a normal size range per age, using the upper limit of the predictive interval as the parameter of interest as a cut-off for normalcy. There was no significant interaction of gender and age for all three pineal gland parameters (width, height and area). Linear regression analysis gave 99% upper prediction bounds of 7.9 mm, 4.8 mm and 25.4 mm², respectively for width, height and area. The slopes (size increase per month) of each parameter were 0.046, 0.023 and 0.202, respectively. Ninety-three percent (95% CI 66–100%) of asymptomatic solid pineoblastomas (data on pineoblastomas from chapter 7) were larger in size than the 99% upper bound.

The aim of chapter 10 is to assess size and morphology of the cystic pineal gland in children (0-5 years) and compare the findings with published pineoblastoma cases. In this retrospective multicenter study 257 MR examinations (232 children, 0-5 years) were evaluated regarding pineal gland size (in a similar fashion as in the previous chapter width, height and planimetric area, and this time also the maximal cyst size) and gland morphology. We performed linear regression analysis with 99% prediction intervals of gland size versus age for the size parameters. Results were compared with a data on pineoblastomas from the meta-analysis presented in chapter 7. Follow-up was available in 25 children showing stable cystic findings in 48%, cyst size increase in 36% and decrease in 16%. Linear regression analysis gave 99% upper prediction bounds of 10.8 mm, 10.9 mm, 7.7 mm and 66.9 mm², respectively for cyst size, width, height and area. The slopes (size increase per month) of each parameter were 0.030, 0.046, 0.021, and 0.25, respectively. Most of the pineoblastomas showed a size larger than the 99% upper prediction margin, but with considerable overlap between the groups.

Chapters 9 and 10 present age-adapted normal values for size and morphology of the cystic and non-cystic pineal gland in children aged 0 to 5 years. Analysis of size is helpful in discriminating normal glands from (cystic) pineal pathologies like pineoblastoma. In addition chapter 10 presents guidelines for the approach of a solid or cystic pineal gland in hereditary retinoblastoma patients.


